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THREE NOTABLE NINETEENTH-CENTURY PSYCHIATRISTS OF WARWICKSHIRE*

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I AM going to give sketches of the lives of three notable nineteenth-century psychiatrists who were associated with and lived in my own county of Warwickshire.

I. JOHN CONOLLY

John Conolly was born in 1794 at Market Rasen. His father died when he was six, and he had an unhappy childhood and schooling, boarded out with a widow. His step-father was a political *émigré*, who taught him French.

When eighteen he enlisted in the Cambridge Militia. Four years later he married and then spent an idyllic year in a cottage on the Loire. When they had a baby he had to earn a living, and so in 1817 he entered Edinburgh as a medical student, and later studied in Paris.

He practised medicine at Lewes for a few months and then moved to Chichester for a year, thence to Stratford-on-Avon, where he was appointed "Inspector of Lunatic Houses for the County of Warwick", and founded the local Provident Dispensary. Though active civically, being Alderman, twice Mayor, and one of those responsible for saving Shakespeare's tomb, he was less successful in his practice and never earned more than £400 a year.

In 1827 he was appointed the first Professor of Medicine in the University of London. It has been suggested that he was given this high-sounding appointment through the improper influence of Lord Brougham, one of the joint founders of the University. But, in fact, the men appointed to the fourteen initial chairs were all young and obscure, and mostly from over the border, since the emoluments were small—the total University outlay on all

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salaries being only £7,500—and security tenuous. Perhaps he was considered because while at Stratford-on-Avon he had been a friend of Dr. Samuel Parr, Vicar of Hatton, an eccentric, interested in the foundation of the University, who died in 1825.

Parr is a minor historical figure, sometimes described as the Whig Dr. Johnson, though he seems to have had all Johnson's bad qualities and few of his good ones, being bad tempered, clumsy, discursive, disputatious, gluttonous, inconsiderate, pedantic, and verbose.

Conolly's inaugural lecture at London University was a great success. He tried in vain to introduce the teaching of psychiatry into the medical curriculum. In 1831 he suddenly left and set up in practice at Warwick, being again appointed Inspector of the half-dozen lunatic houses.

Conolly described the conditions of patients in private mental hospitals in his books. As he has been accused of exaggeration I quote Gardiner Hill's description, which is in similar terms: "In the early part of the present century lunatics were kept constantly chained to walls in dark cells, and had nothing to lie upon but straw. The keepers visited them, whip in hand, and lashed them into obedience; they were also half-drowned in 'baths of surprise'; some patients were chained in wells, and the water made to rise until it reached their chins. One horrible contrivance was a rotatory chair in which patients were made to sit and were revolved at a frightful speed." They were chained to their beds and left from Saturday afternoon to Monday without attendance and with only bread and water within their reach.

Conolly recommended such reforms as a state-owned lunatic asylum for each town, with a medical superintendent and assistant doctors, adequate pay for attendants, occupational therapy, frequent visits by friends, and community care. In 1838, having unsuccessfully competed for the post of Resident Physician at Hanwell Asylum, he moved to Birmingham to teach at the Queen's Hospital, but shortly afterwards applied again to Hanwell, and was appointed. The Middlesex Asylum at Hanwell, with its 918 patients, was the biggest in the country, but control was divided between the committee, superintendent, two assistant medical officers, matron, and steward. Conolly, a disciple of Pinel, and familiar with the work of Gardiner Hill and Dr. Charlesworth at Lincoln two years before, was resolved to end mechanical restraint. Although the visiting justices supported him, he was worried by their noisy brawling at committee meetings, and remarked that the most disturbed patient in a distant part of the asylum seemed to know at once what had transpired. His other supporter was the matron, Miss Powell, to whom he paid a touching tribute. The rest of the staff opposed him, the medical officers on the grounds of his inexperience, so he was obliged to resort to subterfuges and declared that one of them—Dr. Button—was redundant; but as soon as he had gone he discovered that he needed a substitute, and appointed Dr. Davey. On 21 September, 1839, he abolished all mechanical restraint at Hanwell—a remarkable achievement when we consider that he had only arrived on 1 June.

His main work was now done: within twelve years he popularized his non-restraint system, which included the proper moral treatment of the patients, good buildings, occupational therapy, forbearance, and consideration for the individual. A question that arises is where he had learned his psychiatry. Probably when he stayed in Paris after qualification he spent much of his time at Bicêtre, and so was able to familiarize himself with Pinel's work.

He was a great founder of societies, e.g. the Warwick and Leamington Phrenological Society (1834), in the days when this science was preparing the ground for our ideas on gross brain pathology and localization, and before its later fashionable extravagancies; and, with Forbes and Hastings, the Provincial Medical Association, now the B.M.A. It has been suggested that he was a man of short-lived enthusiasms, but on things that really mattered he showed plenty of persistence in spite of opposition and his own poor health, for he suffered from tic douloureux.

He was a man of slim figure and attractive appearance, with dark curly hair and an interesting, sympathetic and humorous face. He had great charm, and was a fluent and lucid speaker and writer. He died in 1866 with a terminal hemiplegia.

II. SIR JOHN BUCKNILL

John Charles Bucknill was born at Market Bosworth in Leicestershire on Christmas Day, 1817. He was educated partly at the local grammar school and partly at Rugby School under Dr. Arnold, whom he did not admire. Thomas Hughes, five years his junior, has described the life in *Tom Brown's School-days*, though I do not suggest that Bucknill was the model for Flashman.

Bucknill studied medicine at University College and Hospital and qualified in 1840. At the age of 27, owing to poor health, he was advised to live in Madeira or in the West Country, and obtained the post of Medical Superintendent at the new county asylum at Exminster.

The treatments he advocated included antimony for mania, phosphorated oil for dementia, chloroform for chorea, morphia, until it was replaced by chloral hydrate, and tracheotomy for epilepsy. He was, however, thoroughly progressive, and boarded out suitable women patients. In 1852 he founded the *Asylum Journal* (now the *Journal of Mental Science*), though the first number did not appear until 1853. He edited, and wrote a good deal of it himself; it was printed in Exeter, and his son used to have to gallop with the proofs, to the printers and back, on his half-wild Exmoor pony. He took his M.D., and in 1859 was elected F.R.C.P., where he was also Censor and Lumleian lecturer. He was later elected F.R.S.

He was President of this Association in 1860. His address reviewed the position of lunacy, and he made the acute remark that "The public extends its unreasonable antipathy to the insane, to all those who are connected with insanity, even to those who wrestle with the great evil." He deplored the fact that though 18,000 pauper lunatics were in asylums, 14,000 were maintained elsewhere—under the Poor Law and outside the control of the magistrates.

He did a good deal of legal work, and in an article on medical certificates of insanity he pointed out that the certificate may have to be justified in Court. In 1860 he anticipated the mental health tribunals now about to be set up by recommending to the Select Committee on Lunatics that the patient should be examined by an independent psychiatrist. In his valedictory address to the Association, he suggested informal admissions, community care of chronic patients who had passed the acute phase of their illness, and pensions for asylum officers. He deplored the frequency of casualties to patients owing to drunken attendants, and Committee interference with the authority of the metropolitan medical superintendents, as opposed to the relative autonomy of their provincial colleagues.

In 1862 he retired from Exminster to become a Lord Chancellor's Visitor.

With Hack Tuke he wrote the standard *Manual of Psychological Medicine* (1858). He published the *Psychology of Shakespeare* (in 1859), which consisted of studies of various characters, including Hamlet, whose madness he found to be both real and assumed, in accordance with our modern view. A second edition was issued (in 1867) as *The Mad Folk of Shakespeare*. He was a joint founder of *Brain* in 1878, when he also published his *Habitual Drunkenness*. He regarded alcoholism as a cause and not a consequence of disease, and considered that an alcoholic could stop drinking by a mere effort of will. In this I think he had been unduly influenced by an early impression, for when he was at Rugby School there was a clever amusing drunkard, who used to entertain the boys with music and legerdemain in the dining halls. After a heavy debauch he made a bet of one guinea with the old school doctor, that he would not get drunk again for a twelvemonth, and he won it. He waited until midnight of the last day, pocketed his bet, and was never sober again, for he quickly drank himself to death. Bucknill also tells the story of the countryman who had hurt his eyes by drinking and went to an oculist for advice. He found him at table with a bottle of wine in front of him. "You must leave off drinking," said the oculist. "Why?" said the countryman, "You don't, and yet your eyes are none of the best." "That is true, my friend," replied the oculist, "but then I love my bottle better than my eyes."

In his *Care of the Insane* (1880) Bucknill divided the recent history into a period of abuse from 1828 to 1845, and of reform from 1845 to 1880, and advocated special institutions for dangerous patients, and the successful open door policy of two contemporary asylums. He regretted that, although up to the end of the eighteenth century only those dangerous to themselves or others were sent to asylums, now the milder cases were being admitted; but in this he was vainly protesting against a trend which has continued for the last 150 years. He advocated the single care of private patients. This book is mainly an attack on the abuses of private asylums. Our own library copy formerly belonged to Dr. Hayes Newington, the licensee of Ticehurst House, and its margins are scored with his angry comments!

Perhaps Bucknill exaggerated the abuses, for Lord Shaftesbury did not find such complaints well founded, but even the great Conolly was found in a court case to be receiving 15 per cent. of the fees paid by a private patient to the asylum to which he had sent him, and we may think that this would hardly be approved of today, but is it essentially different from the case of the doctor who sends a patient to his own nursing home?

It is impossible to appreciate the state of lunacy in the nineteenth century without some knowledge of Lord Shaftesbury (1801-1885) and his work for the oppressed.

The only early legislation was the Act of 1744 empowering justices to have dangerous cases apprehended, and an ineffectual Act of 1774 to regulate private asylums. But in 1808 an Act was passed to permit the building of county asylums. In 1828 Shaftesbury, then Lord Ashley, joined the fray and introduced a bill to provide commissioners for the metropolitan district; it was passed in 1829, and he became unpaid Chairman of the Commission until his death. The correction of abuses was due to him more than to anyone else, but he was a doughty champion of the managers and staffs of asylums when they were unjustly attacked. Bucknill wished a magistrate to be obligatory for the

certification of private patients, and this was provided for in Lord Selborne's Lunacy Amendment Bill of 1885, but Shaftesbury was so upset at the idea, since he preferred medical certification alone, that he offered to resign his post. However, the bill was dropped and he resumed the chairmanship shortly before his death. Echoes of this controversy were still reverberating at the passage of the Mental Health Act of 1959. It is interesting to read in Philip Massinger's play, *A New Way to Pay Old Debts*, first acted in 1626, that when Sir Giles Overreach goes mad, although harmlessly, no doctor is called, but the Justice says: "Take a mittimus and carry him to Bedlam," although this was a hundred and twenty miles away.

Bucknill had married Mary Ann Townsend of Hillmorton Manor, Rugby, in 1832, and on the death of his father-in-law he went to live there, whilst maintaining his town house in Wimpole Street. He was one of the Visiting Justices of the Warwick County Asylum, Hatton, from 1874 for a dozen years.

In 1852 he had founded the Exeter and South Devon Volunteers. He was the first recruit and served in the ranks throughout, refusing all promotion. It formed the nucleus of the present volunteer system, and this is probably the main reason why he was knighted (1894).

Bucknill stood 6 feet 1½ inches, and with his penetrating eyes, long beard, frock coat, top hat, and authoritarian manner, he was an imposing and forbidding figure. If a patient made a long rambling speech to him he listened in silence and then ejaculated a loud "Ah" (with rounded lips), to the merriment of his professional colleagues, though whether the patient found it equally amusing is not recorded. As will have been gathered, like Benvolio, "his head was as full of quarrels as an egg is full of meat", and he loved equally a quiet argument or a fighting and noisy debate. His family found him demonstrative in wrath but not in pleasure, and they said that he was a difficult man to understand. He died of catheter fever in 1897, and is buried at Clifton-on-Dunsmore.

III. WILLIAM HENRY PARSEY

William Henry Parsey, the son of a Foreign Office official, was born on 3 April, 1821. He received his medical education at King's College Hospital and was trained in lunacy by Conolly at Hanwell and then under Bucknill, who made him his first assistant medical officer at Exminster in 1844. In 1851 Parsey was appointed Medical Superintendent of the new Warwick County Asylum at Hatton.

In his First Annual Report to the Visiting Justices, delivered 28 December, 1853, he advised separation of mental defectives from the insane, and pointed out the importance of early treatment. He continued: "In the general management of the patients it has been my desire to carry out the system so happily commenced by Pinel in France and developed by Gardiner Hill, Charlesworth, Tuke, and Conolly in this country where its beneficial influence in adding to the tranquillity and comfort of the insane, in reducing their mortality and promoting their recovery is now almost universally recognized. This system does not consist in the mere abolition of mechanical restraint, but in the endeavour systematically to develop and strengthen the better feelings of the patients, in providing them with such occupation and recreation as are suitable to their different capacities, in stimulating them to active and useful exertion, in introducing among them social comforts and in making them as far as possible feel that they are treated as responsible

agents. By means such as these the recovery of many patients is secured with very little aid from the administration of drugs, but to secure so desirable a result the physician has to depend not so much on his personal exertions as on his being able to command the services of an efficient body of assistants able and willing to carry out his instructions." What can we add to this passage today, except to substitute "locked doors" for "mechanical restraint"?

His administration gained the approval of Dr. Conolly on his visits, and there are many statements by the Commissioners to the effect that the instruments of coercion are not to be found. I believe that Hatton was the first asylum where mechanical restraint was never used.

In 1871 he opened an Idiots' Asylum, in which he established a school two years later.

He noted the value of statistics in comparing the results at different asylums.

When the number of patients in the asylum reached 680, he opposed further extensions, preferring a separate institution so that the patients could each have enough care from the Medical Superintendent. He advocated better provision for criminal lunatics and the abolition of observation wards—a reform which I achieved for the Midlands in 1948.

In 1876, in his long and thoughtful presidential address to this Association, he commented that Pinel and his disciple Conolly had established that environment did affect patients, and that although occupation and humanity were now the rule, the giving of responsibility to the patient followed tardily. He advocated the abolition of locked doors, a reform which I only completed for him eighty years later.

Parsey was a well-proportioned, bearded man of just below middle height, to be seen wearing a dark suit and flat-topped bowler hat. Naturally he was proud of his achievements, and there is a tradition that, on his return from holidays, he arranged for the asylum brass band to meet his carriage at the gates, and play him up the drive to the tune of, "See the Conquering Hero Comes". Members of his family have disputed this with me, saying that it was out of keeping with his modest demeanour. Perhaps he was one of those doctors who are lions in the asylum but lambs in the medical superintendent's quarters! However, he seems to have had a sound grasp of the principles of administration, for when there was a general concern at the failure to keep asylum staff for more than a year or two, his stayed with him for decades, and he was proud of having their affection, saying: "I allow every one of them to look up to myself, not as their head, but as their personal friend and adviser."

It may be asked why, as well as describing Conolly and Bucknill, who were "leaders of the people by their counsels, and by their knowledge of learning meet for the people, wise and eloquent in their instructions . . . and that have left a name behind them", I have also described Parsey, a lesser figure. But he can be counted as one of those "merciful men, whose righteousness hath not been forgotten", and I think that we should praise him too lest it be said: "And some there be which have no memorial."

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THE TREATMENT OF PROLONGED INSULIN COMA*

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INTRODUCTION

THIS thesis gives an account of the use of cortisone and adrenocorticotrophic hormone (ACTH) in the treatment of prolonged comas occurring in the course of deep insulin coma treatment. Cases in which neither hormone was used are also included. The pathology and aetiology of this type of prolonged coma are discussed and a classification of the cases seen is made.

The account is divided into nine parts:

- I Normal insulin coma: biochemistry.
- II Prolonged insulin coma: types, former treatment, aetiology, pathology.
- III Experimental treatment: case material, treatment method, laboratory investigations.
- IV Results and their evaluation.
- V Biochemical findings.
- VI Summary of treatment method.
- VII Conclusions.
- VIII Summary.
- IX Appendix: protocols.

From 1949 onwards my assistance was sought from time to time when patients undergoing deep insulin coma treatment, after being given glucose to interrupt their coma, either recovered with difficulty or failed to recover and a prolonged coma ensued. Previous studies (Thorley and Kay, 1951; Kay and Thorley, 1951) suggested that there might be abnormal states of blood electrolytes in these cases, possibly related to adrenocortical dysfunction. Clinical observations indicated that a deficiency of the coenzymes derived from B-vitamins might be an important factor. Experience soon showed that although electrolyte disturbances and B-vitamin deficiencies were present, their correction was not an adequate answer to the problem of arousing a patient from prolonged hypoglycaemic coma.

Observations on two successive cases (Cases 2 and 3) in which coma lasted almost 4 weeks in the first and over 2 weeks in the second, led me to the conclusion that it was imperative to prevent lapses into hypoglycaemia in the early stages of treatment. As glucose administration alone did not do this, and it was thought that the lapses might be due to the unopposed action of insulin, it was decided to try the effects of cortisone and/or ACTH, both of which have anti-insulin effects and can raise and maintain blood-glucose levels.

* Thesis approved for the Degree of Doctor of Medicine in the University of Manchester.

Of the complications that beset deep insulin coma therapy, perhaps the most disconcerting, and by far the most serious, is the failure of the patient to emerge from coma in response to the usual method of "interruption". Each such case is potentially fatal. Lester (1939), quoted by Kalinowsky and Hoch (1953), calculated that a prolonged coma occurred once in 1,877 individual treatments and found that the death rate in 25 cases was 16 per cent. In a large series of insulin-treated cases he found that the death rate due to prolonged coma was 0.33 per cent. Kinsey (1941) in a collected survey of 12,234 cases treated with deep insulin coma attributed 38 deaths (0.31 per cent. of cases) to protracted coma, irreversible coma, hypoglycaemic shock and hyperinsulinism. In a series of 5,882 coma treatments administered to 108 patients, Goldman (1940) reported 23 prolonged ("post-hypoglycaemic") comas, i.e. one (0.4 per cent.) in 256 treatments in 17 per cent. of the patients.

In the series of 62 cases of prolonged coma on which this report is based, it has not been possible to calculate the rate of incidence of prolonged coma in relation to total coma treatments. A rough estimate would be one prolonged coma to 2,000 normal ones. The cases have been collected from thirteen hospitals over a period of three and a half years and it is impossible to assess accurately the total number of coma treatments and of patients undergoing treatment. Not all prolonged comas occurring in these hospitals were brought to my notice, but only those not responding to the usual methods of treatment. There were 4 deaths (6.45 per cent.), a rate about two and a half times better than that found by Lester.

I. NORMAL INSULIN COMA

Biochemistry

According to Thorley and Kay (1951) and Kay and Thorley (1951), there is an orderly sequence of changes in blood components during deep insulin coma. The blood glucose rapidly falls to and is maintained at a low level, about 30 mg./100 ml.

The serum potassium, chloride, bicarbonate and inorganic phosphate fall. The first three remain low, but the phosphate increases when the clearance of glucose from the blood ceases. The falls in serum potassium and phosphate can be related to the removal of glucose from the blood. If there is any attempt to recover in the prodromal stages, further falls in potassium and phosphate occur, probably owing to the removal of more glucose from the blood following attempts at restoration of the blood glucose by gluconeogenesis.

In contrast with the four components mentioned above, the serum sodium and proteins increase. This may be attributed to dehydration as the coma proceeds, since both components fall to a lower concentration after interruption. The loss of fluid, especially by sweating, probably accounts for the progressive fall of serum chlorides and to some extent of serum bicarbonate. The latter may be due to accumulation of organic acids normally metabolized to water and carbon dioxide, but whose destruction is retarded by the interruption of normal metabolism in deep coma. This is supported by the increase in serum base-acid difference as coma proceeds (Kay and Thorley, 1951).

Bliss, Migeon, Nelson and Samuels (1954) have shown that the blood corticoids increase during coma, whether through extra secretion or non-usage is not determined. The increase in corticoids could account partly for the fall in serum potassium and increase in serum sodium; on the other hand it could not account for the falls in serum chloride and bicarbonate. There is some

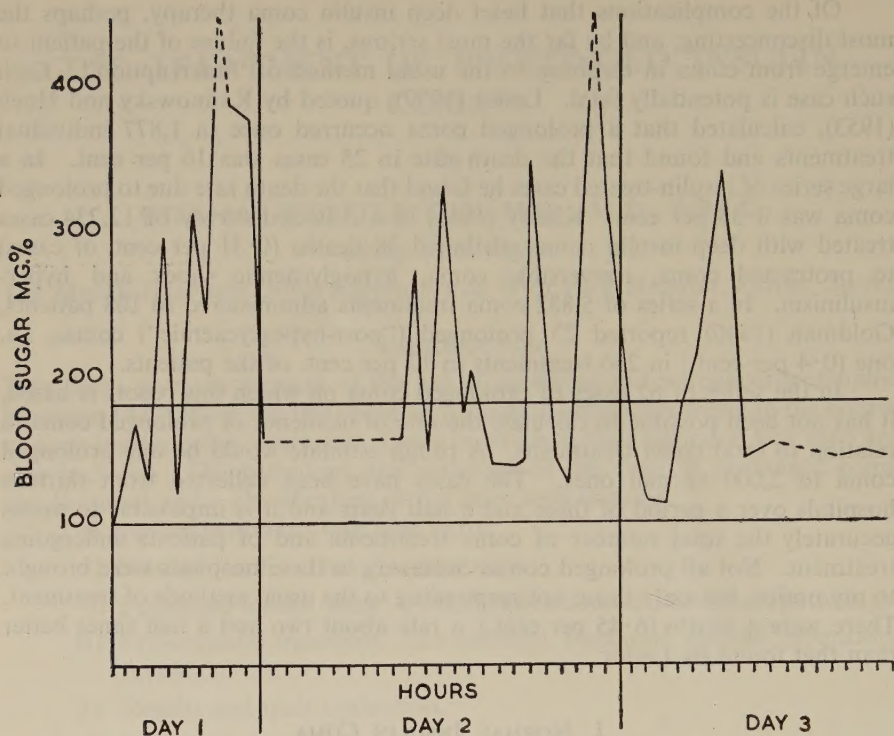


FIG. 1.—Blood sugar in early stages of prolonged insulin coma. Case 2.

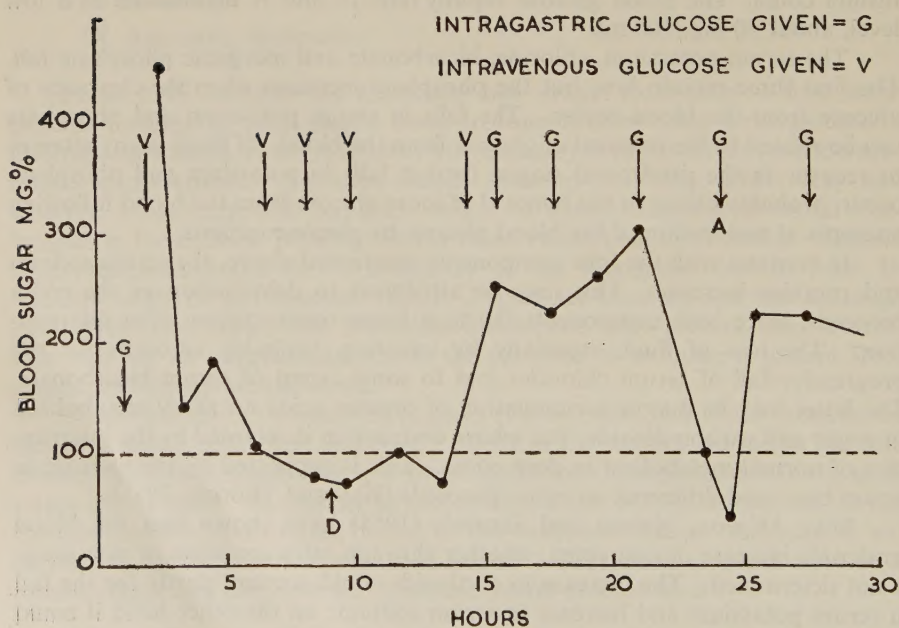


FIG. 2.—Blood sugar in early stages of prolonged insulin coma. Case 3. At D, coma deepening.

evidence that the corticoids are ineffective at coma-producing levels of hypoglycaemia (Kay, 1958).

In the early stages of hypoglycaemia, there is a fall in blood adrenalin (Weil-Malherbe, 1954). There is an increase in blood corticoids which appears to be ineffective and there are paradoxical changes in blood chemistry as the coma proceeds. It is evident that the high dose of insulin breaks down the body's natural defensive mechanisms to produce a continuing state of hypoglycaemia accompanied by adynamogenesis and a state of minimal metabolic activity, which by some workers is described as "near death".

On giving glucose to interrupt coma, several concomitant events occur. The blood glucose is raised to normoglycaemic levels or over, and this stimulates the production of adrenalin (Weil-Malherbe, 1954) and brings the anterior pituitary and adrenal cortex into action (Reiss, Hemphill, Early, Maggs, Cook and Pelly, 1951; Kay, 1958). Normal metabolic activity is also restored. The restoration of normal endocrine activity is the main factor in the maintenance of the normal metabolism and with it the state of normal mental activity. Other factors are involved in the restoration of normal metabolism, e.g., the presence of adequate co-enzymes, etc. These play their part, along with endocrine activity, and with the failure of the latter may be involved in causing prolonged coma.

II. PROLONGED INSULIN COMA

Types of prolonged insulin comas

Various authors have attempted to define and classify the types of prolonged insulin coma, and various descriptive names have been given such as "continued hypoglycaemia", "delayed awakening", "post-hypoglycaemic coma", "hyperglycaemic coma" and so on. The term "irreversible coma" has gradually been dropped for the general term "prolonged coma", since strictly "irreversible" should mean "fatal". None of these classifications appears to have helped to guide treatment.

For the purpose of this thesis, the term "prolonged insulin coma" has been adopted, since it simply means those cases which failed to recover from insulin coma by the usual methods of treatment and which I was asked to see and treat. When seen, some had hypoglycaemia, some hyperglycaemia; some had transiently recovered from coma and relapsed, some had not recovered at all and continued in coma. The facts common to them all were that they had had a deep insulin coma and in spite of attempts to rouse them they were still in coma when I first saw them, sometimes many hours after the first attempt at interruption.

There are a number of symptoms associated with prolonged coma, not all of which may be present in any one case, except, of course coma: hyperventilation with hyperpnoea and/or tachypnoea; motor excitement; rigidity; spasms of extremities and opisthotonus suggestive of tetany; dilated or contracted pupils, usually varying with the glycaemic state; fever, sometimes high. By appropriate laboratory examinations the following can be detected: haemoconcentration; leucocytosis with marked increase in polymorphoneutrophils; hypo- or hyper-chloraemia; loss of plasma bicarbonate. It is frequently assumed that the hyperventilation leads to alkalosis and tetany. In my experience this is rare; it is the loss of plasma bicarbonate that underlies the hyperventilation and the latter does not compensate for the acidosis.

In my experience the possible types of prolonged coma cannot be satisfactorily differentiated on clinical evidence alone. In the present series, however, four types have been encountered:—

- (A) a failure to respond to a maintained hyperglycaemia;
- (B) a state of intense dehydration with normo- or hyper-glycaemia;
- (C) a state of subnormal glycaemia;
- (D) a state of grossly fluctuating glycaemia with a corresponding fluctuation of the coma state.

In any of these four types, abnormalities of blood chemistry may occur, of which loss of blood bicarbonate is the second commonest and perhaps the most important. Of the four types, the last is by far the commonest in the series now reported. Probably this is because cases of the first three types recover fairly easily, often with haphazard treatment, and have not been brought to my attention.

Review of treatment of prolonged insulin coma (excluding the use of ACTH and cortisone)

The aetiology and pathology of prolonged coma are not fully determined. The factors involved are numerous and not all related causally to each other. As a result, treatment has never been systematized. A further difficulty is that not many doctors see more than one case. A doctor faced with a case of prolonged coma may not have had to deal with one before. He has then to depend on his book-knowledge, with or without the help of equally inexperienced colleagues. Should his patient recover, he is ineffably relieved and apt to ascribe the recovery largely to the last therapeutic measure he applied. Should his patient not recover, he may esteem all the measures taken as valueless and those not taken as at least worth trying should he have to deal with another case. Probably to this sort of reasoning is to be attributed the many lines of treatment listed in text books and amplified by verbal advice.

Undoubtedly, the first essential treatment is to raise the blood glucose level by intravenous infusion of glucose solution, usually $33\frac{1}{3}$ per cent. in physiological saline. How often this should be repeated is disputed. The guiding principle should be to maintain a glycaemia at least above normal and control it by repeated blood sugar estimations. Surprisingly enough, few doctors have the blood glucose level determined; treatment is thus carried out blindly.

Basing his observations on over 30 cases of prolonged coma, Biskupski (1954) claims that the repeated injection of 300 ml. of $33\frac{1}{3}$ per cent. glucose-saline intravenously every two hours, plus a rectal drip of 5 per cent. glucose-saline and warm blankets around the patient in bed, gives in nearly every case, recovery in two to six hours. In one of his cases coma lasted 30 hours, because the treatment was not started immediately. In the series now reported, adequate intravenous glucose had been given in almost all cases without effecting recovery; I was only called when this type of treatment had failed. In my experience, when adequate laboratory investigations are done, there is no evidence that saline is absorbed from a rectal drip, and very little evidence that glucose is. The rectal route is therefore not used.

Other recommended forms of treatment are lumbar puncture; electro-convulsion, metrazol-induced convulsion, convulsions induced by coramine; blood transfusion; administration of adrenalin, thiamine, nicotinic acid, calcium salts, potassium chloride, saline solutions of varying strength, cortin, atropine,

singly or in various conjunctions. Many of these had been tried without effect in the present series of cases before I was called upon. None of the measures listed can be regarded as reliable or effective. Some are even dangerous; a few have a useful place in treatment when their need has been demonstrated by chemical tests. It is odd logic to add the insult of a convulsion to an already damaged brain in the expectation of restoring cerebral function.

Not all of these therapeutic measures can be dismissed as useless, although most are discredited. Vitamin-B administration helps in those cases where there is a vitamin-B deficiency but not in others. Additional glucose is only necessary if there is hypoglycaemia; if there is hyperglycaemia, it may aggravate the patient's condition. Large quantities of fluids help if there is dehydration, but may cause pulmonary oedema if there is normal hydration. Intravenous saline is almost always needed, usually as a vehicle for glucose. Venesection seems irrational unless it causes enough shock to jolt the pituitary-adrenocortical system into activity. If blood transfusion helps, it may be because the blood, especially if fresh, contains adrenocorticotrophic and adrenocortical hormones.

Goldman's (1940) advocacy of adrenocortical extract was disregarded probably because of the variable potency of available preparations. I regret that Goldman's work only came to my notice during the process of reviewing the literature for this thesis.

As the purpose of this thesis is to give an account of personal experience of a new and systematized approach to the treatment of prolonged insulin coma, it is proposed not to discuss recorded methods of treatment any further. Whatever form of treatment is applied, three things are essential:

- (i) to restore and maintain the blood glucose level to at least the physiological range;
- (ii) to support and maintain the circulatory and respiratory mechanisms;
- (iii) to control and manage fits.

To these basic essentials is to be added some form of treatment aimed at restoring consciousness.

At any time a sudden circulatory collapse, with or without respiratory collapse, may occur and will call for heroic efforts to combat it and keep the patient alive. In comas extending beyond, say, twenty-four hours further measures must be taken

- (a) to control the blood chemistry, especially the electrolytes,
 - (b) to feed the patient,
- and (c) to prevent pneumonia.

Aetiology of prolonged insulin coma

Although, as has been said, the aetiology of prolonged insulin coma is not settled, certain facts are established by clinical experience and pathological investigations.

(1) B-vitamin deficiency. Some patients undergoing deep insulin coma therapy show signs of B-vitamin deficiencies as their coma course progresses: paraesthesia, tingling of fingers and feet, tenderness and weakness of muscles, clumsy hand movements, e.g. when dressing, slight ataxia, red, sore tongue, angular stomatitis, scaly roughness, pigmented sometimes, of the backs of the hands and feet. This deficiency, especially of thiamine, has been attributed to

the necessity to metabolize the unusual amounts of carbohydrate given during the treatment course.

In due time, these patients are sluggish in recovering from coma and eventually may fail to respond to glucose administration and have a prolonged coma in spite of a sustained high blood glucose (see Case 1). They belong to Type A above. In cases where the vitamin deficiency was diagnosed, administration of B-vitamin complex has abolished the signs of deficiency and enabled the patients to complete their coma course without further difficulty. It was soon found that cases of prolonged coma of this type were exceptional and, in any case, the use of vitamin-B supplements prevented them.

In a few cases, it was possible to investigate the blood electrolytes, lactate, pyruvate and co-carboxylase before and after administration of B-vitamins. The following case illustrates this.

Case (a) A.H. Female aged 31. Had had 14 comas. Coma dose of insulin 60 units i.v. Roused with difficulty after intravenous glucose. Complained of numbness of fingers and back of head, and difficulty in controlling hand actions in dressing. Hands had to be watched to "see they went into the right place". Skin on backs of hands rough; lips sore; tongue edges red. These suggested B-vitamin deficiency. The patient was therefore treated with full doses of mixed B-vitamins. In one week's time the symptoms complained of had disappeared completely and the physical signs almost. The blood chemistry before and after treatment is given in Table I. There was normal gastric acidity. The coma course (39 comas in all) was completed without further difficulty.

TABLE I
Blood chemistry in thiamine deficiency
Case (a)

Serum:				Normal range	Before	After
Sodium	mN	..	..	135-150	150	150
Potassium	mN	..	..	3.6-5.1	4.6	—
Chloride	mN	..	..	95-105	103.4	—
Bicarbonate	mN	..	..	25-35	26.5	26.5
Inorganic P	mN	..	..	0.6-1.6	1.4	1.5
Blood:						
Lactate	mg./100 ml.	..	..	6-18	14	13
Pyruvate	mg./100 ml.	..	..	0.5-1.2	1.2	0.5
Co-carboxylase	µg./100 ml.	..	..	5.0-12.0	5.2	12.5

"Before" = when first seen and before treatment with vitamin B was started.

"After" = after 7 days' treatment with B-vitamins and rest from coma treatment.

(Note: mN = mEq./lit.)

(2) Water loss. Some patients lose large amounts, e.g. 3-5 litres of water during a coma. Although this is a common experience, I have verified it by weighing patients before and after coma. An undue loss of fluid may lead to a prolonged coma with dehydration—type B; but as all who lose a lot of fluid in coma do not have a prolonged coma, some other factor or factors must also play a part in causing the prolonged coma of type B. (Case 6.)

(3) Failure to maintain carbohydrate intake. Some patients, roused by the usual method of interruption, relapse through failing to maintain their intake of carbohydrate. They may refuse their breakfast or vomit after taking it; they may even vomit their intra-gastric glucose. After a period of stubbornness and confusion, they may relapse into sopor and into coma, if not treated at once with intravenous glucose. Usually prompt and adequate intravenous administration of strong glucose solution rouses them, but it is as well to

continue the infusion till they are well awake and to give them glucose drinks followed by breakfast again. These patients correspond to type C. (Case 5.)

(4) Sensitization to insulin. During their course of insulin comas, most patients become more responsive to insulin, a phenomenon generally described as "sensitization". Adequate reduction of insulin dose is usually enough to combat this form of adaptation. However, the sensitization does not always follow a smooth pattern and is affected by recent exercise, intake of carbohydrate and so on. If there is an undue disturbance of such factors, relative overdosage with insulin may occur and be related to the precipitation of a prolonged coma. Type D includes cases arising in this way.

Sensitization may be the result of many factors, but two sets of factors can be identified, one psychological and the other endocrinological. Some patients, possibly through deep unrevealed fears, appear to be able to resist going into coma, in spite of coma-producing blood-glucose levels. If these fears are dispelled they go into coma more easily, require less insulin and appear to be "sensitized". Case (b) illustrates this.

Case (b). A man aged 38 failed to go into coma with doses of insulin up to 800 units given intramuscularly in spite of adequate hypoglycaemia and all its attendant discomforts. Finally, he was given 800 units of insulin intravenously. The prodromata to coma were shortened and his resistance broken through. He went rapidly into a profound coma from which he was aroused by intravenous infusion of glucose solution. When assured that he had "had a coma", he asked if that was "all that it was" and confessed his previous fear. Thereafter he went regularly into coma on an intramuscular dose of 350-450 units of insulin.

Sensitization from endocrine causes is commoner and more complicated. This aspect is more fully discussed later under "Pathology", but some comment may be made here (see also Kay, 1958). Deep insulin coma is a form of stress acting on the endocrine system as an integrated whole, but mainly on the pituitary and adrenal cortex. The effects of stress are first to stimulate and then to fatigue. In an organ already fatigued, stimulation may not occur and fatigue may be intensified to the point of exhaustion. The gradual fatiguing of the anterior-pituitary-adrenocortical axis can be shown by following the changes in the excretion of 17-ketosteroids (Batt, Kay, Reiss and Sands, 1957) and 17-ketogenic corticoids. When this occurs, the main antagonists of insulin become less and less available to the body and the patient becomes sensitized to insulin, in the same way as the patient with Simmonds' or Addison's disease is. The intermittent hyperglycaemia in the recovery phase from coma is likely to stimulate the β -cells of the islets of Langerhans and so facilitate the production of endogenous insulin. (Anderson and Long, 1947a.) These two factors may augment each other to cause the observed sensitization of the patient to insulin.

(5) Formation of loculi of insulin. Another possible factor in sensitization is the formation of loculi of unused insulin given intramuscularly which release insulin in an uncontrollable manner. There has been much speculation as to whether such loculi can occur, but the work of Burkinshaw *et. al* (1958) establishes the possibility of their occurrence. Obviously when insulin is given intravenously, similar loculi are unlikely.

Pathology

(1) Morbid anatomy. As deaths from prolonged insulin coma have to be referred to the coroner, who arranges his own post-mortem examinations, it has not been possible to make any personal investigations in the four deaths in the present series. Lawrence, Meyer and Nevin (1942) have reported on the

pathological changes in the brain in fatal hypoglycaemia and reviewed the relevant literature. Two of their six cases were deaths from prolonged coma in deep insulin therapy for schizophrenia. They found that there was widespread damage, degeneration and necrosis of nerve cells with corresponding microglial and macroglial proliferation, chiefly affecting the cerebral cortex, the caudate nucleus, the putamen, the striate body, the globus pallidus and thalamus. Changes in the brain stem and cerebellum were less marked. Vascular lesions were not present, although other observers have reported them. Lawrence *et al.* attributed the cerebral damage to the interruption of cell metabolism through lack of glucose during hypoglycaemia and coined the word "oxyachrestia" to describe the phenomenon. Kay and Thorley (1951) used the word "adynamogenesis" in the same connection. The cortical damage could account for the difficulty the patient had in making contact with his environment when the coma state had passed off.

(2) Nuclear damage and pyrexia. Early in prolonged coma there is pyrexia, sometimes high, 103–106°F, with polymorphonuclear leucocytosis, which later subside without special treatment. These are very likely due to the cerebral damage. The pyrexia may also be due to the increased metabolism of carbohydrate caused by the unopposed (by gluco-corticoids) action of insulin (c.f. after hypophysectomy and adrenalectomy) and to the effect that the administration of glucose has in raising the respiratory quotient and in increasing the efficiency of insulin (Dohan and Lukens, 1948). In the late stages of recovery, there is marked "hangover", confusion and headache, often severe, resembling a post-concussional state. Very high blood uric acid concentrations are sometimes observed both in normal and prolonged comas. These also may be related to nuclear damage.

(3) Gastric stasis and achlorhydria. Neutral stomach contents are sometimes found at the end of normal comas, but in prolonged comas both gastric stasis, with probable pyloro-spasm, and arrest of acid secretion are very frequently found. Both these may be related to failure of the anterior pituitary or adrenal cortex or both. In interruption by gavage, gastric arrest may be the event which determines the failure to awake from coma, since the glucose feed does not pass into the parts of the intestine from which it can be absorbed to raise the level of the blood glucose. Thus the period of hypoglycaemia is prolonged and a state of prolonged coma may be set up. Once gastric stasis is established, it is not easily abolished since it does not respond to drugs, such as pilocarpine, Mechothane, etc., which normally stimulate gastric and intestinal movement, nor to drugs, such as atropine, which abolish spasm. It may respond to ACTH or cortisone injections (Porrúa *et al.* 1954 and Castro-Rial *et al.* 1954). Often, but not always, resumption of gastric movement and recovery from prolonged coma coincide, or nearly do, thus suggesting that the stasis and prolonged coma may be causally related or have a common cause, such as failure of the anterior pituitary and/or adrenal cortex. Both may be of central nervous origin. On the other hand, the stasis, and the failure to secrete hydrochloric acid which often accompanies it, may also have a local origin in damage to or exhaustion of the nerve plexuses associated with gastric function, caused directly by insulin or mediated by the prolonged hypoglycaemia. In this connection it should be noted that Schereschewsky *et al.* (1929) (quoted by Lawrence *et al.*, 1942), found changes in the sympathetic ganglia in the solar plexus, following death from prolonged hypoglycaemia.

The initiation of gastric stasis may be related to insulin or to increased

secretion of adrenalin, which latter may occur when glucose is given to terminate hypoglycaemic coma (Weil-Malherbe 1954). Insulin in small doses stimulates gastric movement and secretion of acid. It has, however, been shown (Olson and Necheles 1955), that, in the hypoglycaemic phase produced by moderate doses (25 units) of insulin, the volume and acidity of gastric secretion are significantly reduced. When the blood sugar begins to rise, the acidity and volume of gastric secretion rise also. Secretion, if not movement, and glycaemia thus appear to be interrelated. Hypertonic solutions introduced into the stomach reduce gastric motility. The glucose or sugar solutions introduced into the stomach to interrupt coma are very hypertonic, 33 per cent. to 50 per cent. solutions being habitually used. Since prolonged comas are infrequent, it is evident that such hypertonic solutions do not always produce gastric stasis. When there is gastric stasis in prolonged coma, it is likely that there is some factor other than the effect of hypertonic solutions which causes the stasis or which has "conditioned" the stomach and made it unusually susceptible to the hypertonic solution. It is suggested that this factor is most frequently hypofunction or failure of the anterior-pituitary-adrenocortical system.

Prolonged comas may occur even when glucose is given intravenously, at the normal time, to interrupt coma. This occurred in 19 cases (almost one-third) of the present series. Gastric stasis may have been present, it certainly was in some, but it had no part in the failure to terminate the coma by preventing glucose reaching the blood stream. Gastric stasis does not appear to be present in prolonged comas associated with dehydration, since the glucose given by gavage has usually been sufficiently absorbed to rouse the patient were there not some other defect. It seems that gastric stasis, and failure of acid secretion when it occurs, is part of the prolonged coma state, rather than its primary cause, and is referable to hypofunction or failure of the anterior pituitary-adrenocortical system.

(4) Disturbances of blood chemistry. Personal studies, discussed later, have revealed disturbances of blood chemistry in addition to the disturbed glycaemia and dehydration. One very serious disturbance is lowering of plasma bicarbonate, which may contribute to or aggravate the cerebral damage. The corresponding loss of plasma chlorides is usually masked by the intravenous salines used. In addition to the thiamine deficiency previously discussed, there may be a disturbance of the thiamine-using mechanisms, since often an increase of blood pyruvate persists when the blood thiamine level has been raised to normal. A similar condition has been observed in alcoholics with thiamine deficiency, whose blood co-carboxylase has become normal after thiamine medication (Kay, Murfitt and Glatt, 1959).

(5) Fluctuations in glycaemia. More serious, and more enlightening, are the rapid falls in blood-sugar content which occur in the early stages of prolonged coma when glucose is given intravenously to raise the blood sugar (See Figs. 1 and 2). If repeated estimations of blood sugar are not done, or if repeated intravenous administration of glucose at short intervals is resorted to, this phenomenon is not detected. The course of events is as follows. When the patient fails to awake after attempted rousing by the usual method, glucose is given intravenously. This produces a rapid hyperglycaemia, sometimes extreme. The coma is observed to lighten. Soon relapse into deep coma occurs, hypoglycaemia has followed the hyperglycaemia, more glucose is given intravenously and the cycle of events is repeated. If this sequence is repeated, hopefully, often enough, the patient may recover; often he does not.

The explanation of this series of events appears to be that when the induced hyperglycaemia is being reduced by the action of insulin, at normoglycaemic levels the usual mechanisms for arresting the further action of insulin, so preventing hypoglycaemia, do not act; hypoglycaemia again ensues and perpetuates and aggravates the coma.

The mechanisms for preventing hypoglycaemia in the intact person are, broadly:

- (a) the cessation of the secretion of insulin,
- (b) counter-action by the pituitary and adrenal glands and probably the thyroid.

Besides stimulating gluconeogenesis, the outflow of hormones from the pituitary counteracts the peripheral action of insulin in the tissues, and probably inhibits the secretion of insulin (Anderson and Long, 1947b) thus diminishing the uptake of glucose from the blood and mitigating the competition of the muscles with the brain for the available blood glucose, upon which the metabolism of the brain almost entirely depends. In addition, by its hormones the pituitary stimulates the adrenal cortex and the thyroid and appears to have a stimulating effect on the cerebral cortex, either directly or through its effect on other endocrine organs (cf. the euphoria associated often with ACTH or cortisone treatment, e.g. of rheumatoid arthritis). If the pituitary is fatigued or damaged, its actions are abolished or diminished. It does not respond to the stimulus of raising the blood sugar, so that its normal functions, necessary in recovery from insulin coma, are in abeyance. Moreover, the fasting animal, of which the patient in hypoglycaemic coma is a special type, is more than normally sensitive to insulin and less responsive to adrenalin.

(6) Dysfunction of the anterior-pituitary-adrenocortical system. In view of its relationship to some parts of the brain damaged in fatal hypoglycaemic coma, it may be inferred that the pituitary itself is damaged, and/or in a state of dysfunction from lack of stimuli from the rest of the brain, if therapeutic hypoglycaemic coma is unduly severe or prolonged. Pituitary failure or dysfunction may play an important part in the perpetuation, if not in the causation, of prolonged hypoglycaemic coma.

There is evidence of adrenocortical dysfunction at the end of a normal coma. Kay and Thorley (1951) argued that the changes in the blood chemistry at the end of a normal coma are more consistent with the effects of adrenocortical failure than with the effects of adrenocortical stimulation. They suggested "that the adynamogenesis produced by large doses of insulin, especially coma-producing doses . . . inhibits the function of those organs, such as the adrenals, that normally are responsible for counteracting insulin." This view was challenged by Shattock and Micklem (1952), but in interpreting their results they ignored the fact that the patient roused from coma is a relatively intact organism and some of the phenomena they recorded, especially the fall in circulating eosinophils, were most likely due to the effect of hyperglycaemia on the restored anterior pituitary and adrenal cortex (Reiss *et al.*, 1951).

Studies of 17-ketosteroid and corticoid excretion on any chosen day of coma are difficult, because of the proneness to urinary incontinence in coma, and are likely to be inconclusive, because the period of hypoglycaemia is relatively short in relation to the rest of the day, with its many factors that affect steroid output. On the other hand, serial studies of steroid excretion in patients undergoing deep insulin coma therapy, are informative (Batt, Kay, Reiss and Sands, 1957; Kay, 1958). Some results are reproduced in Figures 3, 4, 5. These

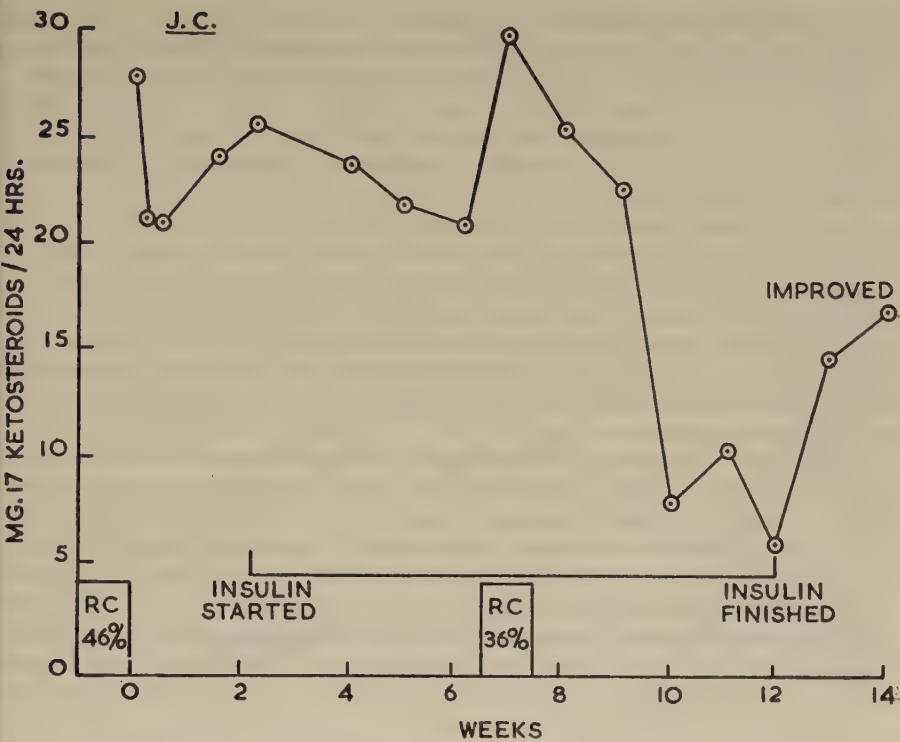


FIG. 3.—Initial values high, final values low. (RC refers to thyroid function.) Steroid excretion in deep insulin coma treatment. (Batt, Kay, Reiss and Sands, 1957.)

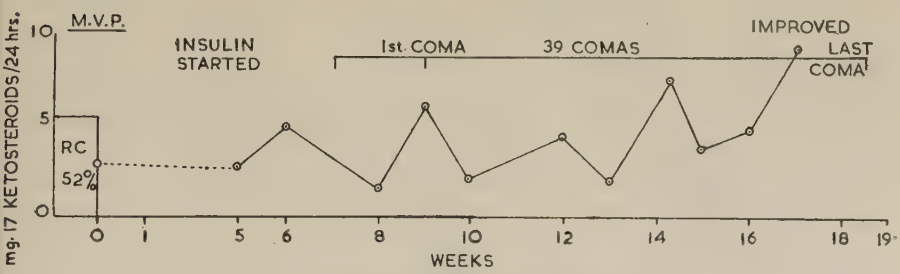


FIG. 4.—Initial values low, final values normal.

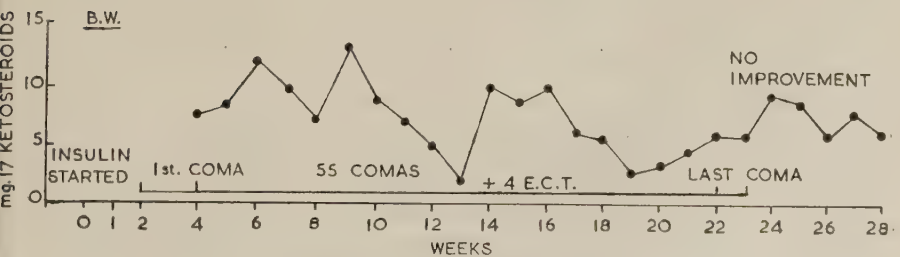


FIG. 5.—Initial and final values low.

indicate that there are various levels of activity of the adrenal cortex, and of the anterior pituitary too, at the start of the treatment course, followed by phases of stimulation and depression of adrenocortical response as the course proceeds. Often there is stimulation in the early stages, fatigue or depression in the middle stages, whilst at the end there may be stimulation or depression. The course of events depends on the initial state of the adrenal cortex and its reserve of reactivity. Further similar studies amplified by estimations of 17-ketogenic corticoid excretion confirm these findings (personal observations).

In the cases of prolonged coma here reported, where it was possible to determine steroid excretion, it was invariably low. Some patients showing difficulty in recovering from coma, especially those going into coma on low doses of insulin, say 40–80 units, were found to have low 17-ketosteroid and 17-ketogenic corticoid excretions. In these cases doctors were usually advised to discontinue coma treatment because of the poor adrenocortical function and the risk of prolonged coma.

From blood corticoid determinations during therapeutic insulin coma, Bliss *et al.* (1954) concluded that the adrenal cortex was stimulated since the blood corticoids increased. Examination of their results shows that they had three types of corticoid response, shown with their average curve in Fig. 6, which were masked by their taking averages. It will be observed that in the hyper-responsive and normo-responsive types there is a tendency for the blood corticoids to fall at the end of coma, whilst the hypo-responsive type shows a state of fluctuating activity of the adrenal cortex at a relatively lower level. In one patient, investigated twice in this work, the level of blood corticoids in the later

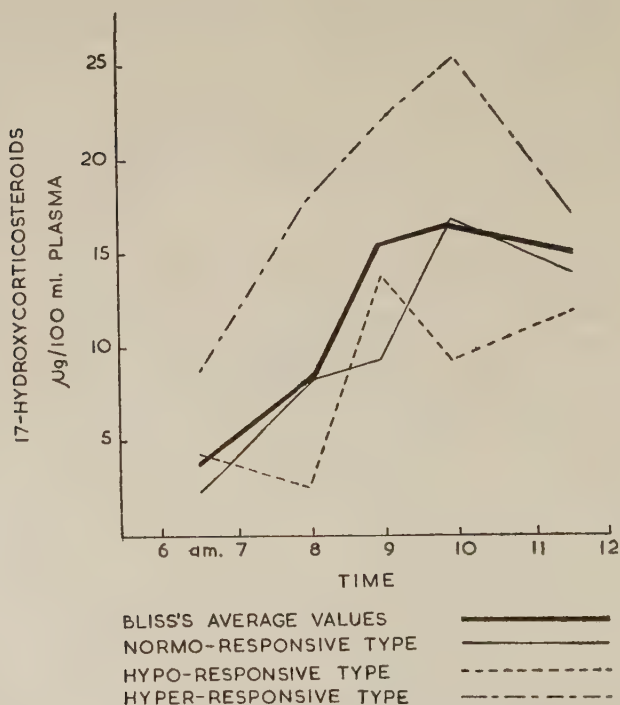


FIG. 6.—Effect of insulin coma on level of 17-hydroxycorticosteroids in plasma. (Bliss *et al.*, 1954 and Kay, 1958.)

coma was lower than in the earlier, suggesting that his pituitary-adrenocortical system was becoming fatigued.

From studies of the effects produced by injected ACTH and cortisone on the patient and on the blood glucose in normal insulin comas, it seems probable that ACTH and the adrenocortical hormones are ineffective in hypoglycaemia (Kay, 1958). This may account for the increase of blood corticoids observed by Bliss: the corticoids secreted were not used and accumulated in the blood. There may not have been extra secretion, especially in the later stages of coma.

The achlorhydria and gastric stasis found in prolonged coma, especially of the fluctuating glycaemic type (type D), have already been related to hypofunction of the anterior pituitary-adrenocortical system.

Goldman (1940), in a patient in prolonged post-insulin coma, observed bronzing of the skin. This suggested to him that adrenal cortical deficiency was an element in the cause of the syndrome. He then began to use adrenocortical extract (Eschatin, Parke, Davis & Co.) and large quantities of saline in treating prolonged insulin comas. Thereafter, no prolonged stupors were observed in spite of the occurrence of 17 post-hypoglycaemic comas. Reporting his success he concludes "These therapeutic observations are probably as strong evidence as can be obtained to support the theory that adrenal cortical deficiency plays the determining role in causing this syndrome." This may be *post-hoc* reasoning, but exactly the same could be said about the cases successfully treated with hormones in the present series. The failures suggest, however, that there may be other not yet determined factors involved in the causation and perpetuation of prolonged insulin comas.

Whether the presumed loss of adrenocortical function is primary or dependent on pituitary failure is not important since the result is the same either way. What is suggested is that there is a probable failure or low state of function of the anterior-pituitary-adrenocortical system in some cases of prolonged hypoglycaemic coma and that this failure or hypofunction may even be gross and continued. It would also account for the phenomenon of sensitization to insulin that frequently occurs during the treatment course.

In prolonged coma, it would appear that, in addition to any residual circulating administered insulin, endogenous insulin is being secreted by the pancreas in response to the hyperglycaemia induced by the administration of glucose, and its secretion is not arrested at normoglycaemia; otherwise the recurrent hypoglycaemia would not occur. In addition, any intramuscular loculi of unabsorbed injected insulin, which slowly drain their insulin into the circulation, could help in producing or aggravating the recurrent hypoglycaemia. Prolonged comas occur even when insulin is given intravenously to induce coma; loculi cannot reasonably be postulated in such cases. The readily available exogenous insulin should eventually be used up by the administered glucose. It seems, then, that the most probable cause of the recurrent hypoglycaemia in prolonged coma is the uncontrolled endogenous secretion of insulin following the repeatedly induced hyperglycaemia. The adrenal cortex, fatigued or exhausted by the stress of the patient's illness, the stress of the prolonged pre-coma state or the repeated stresses of insulin coma treatment, fails to mobilize enough glucocorticoids, both during the coma and in response hyperglycaemia, to cope with the circulating insulin, whether endogenous or exogenous. The adrenal failure may be primary, associated with, or secondary to pituitary failure of similar origin. Such a condition calls for the administration of cortisone or similar adrenocortical hormones to supplement the natural secretion, or of ACTH to evoke a natural secretion from the residual power that even a fatigued adrenal cortex

may have, to assist the impaired physiological regulatory processes that prevent hypoglycaemia.

In so far as the pituitary and adrenal cortex are concerned, prolonged insulin coma bears some relation to wound shock, where the anterior-pituitary-adrenocortical mechanisms are first stimulated and then fatigued and the administration of exogenous hormones is needed to supplement and correct their hypofunction.

(7) *Summary.* My theoretical approach to the problem of prolonged insulin coma of the fluctuating glycaemic type (type D) can now be summarized. Whatever the primary cause of the failure to respond to the usual method of interruption may be, the early stages of the prolonged coma are characterized by hypoglycaemia relapses which aggravate the state. These relapses are probably mainly due to failure to control residual exogenous insulin and endogenous insulin secreted in response to the induced hyperglycaemia. This failure to control insulin at normo-glycaemic levels is referable to failure of the anterior-pituitary-adrenocortical system, due to temporary exhaustion or even damage. Administration of effective pituitary and/or adrenocortical hormones should correct the imbalance between the pituitary-adrenal system and insulin, thus stabilizing glycaemia and establishing conditions for recovery. Supplies of adrenocorticotrophic hormone (ACTH) and cortisone (acetate) were therefore obtained from the Medical Research Council, in April, 1952.

(It may be mentioned here that according to Alexander (1953), Clower and Niswander, in a paper read before the Massachusetts Society for Research in Psychiatry, 2nd November, 1951, reported having given cortisone intramuscularly and by gavage in prolonged insulin coma. Their results are not stated. This information did not reach me until late in 1953 when I had by then used cortisone and ACTH in a number of cases.)

III. EXPERIMENTAL TREATMENT

Case material

By the courtesy of doctors in a number of mental hospitals, I was called to their cases of prolonged coma, preferably as soon as possible after the prolonged coma was diagnosed. This report is based on 62 consecutive cases, 18 male and 44 female, seen and treated in 13 hospitals over a period of 3½ years.

The mean ages of the patients, the mean numbers of comas they had had up to and including the prolonged one and the mean doses of insulin used to induce the coma that became prolonged, are set out in Table II, together with ranges and standard deviations. The sex groups are comparable from these three aspects, the differences between means of ages, numbers of comas and insulin doses not being statistically significant. For purposes of later discussion, therefore, males and females can be treated as one homogeneous group.

TABLE II

Numbers of patients and means of ages, of numbers of comas (including the prolonged one) and of doses of insulin (units)

		Males	Females	All
Numbers of patients	..	18	44	62
Ages:				
means and S.D.	..	29.6±4.96	28.3±6.07	28.7±5.8
ranges		24-39	17-40	17-40
Numbers of comas:				
means and S.D.	..	10.6±9.6	11.8±10.2	11.4±10.0
ranges		1-35	1-38	1-38
Insulin doses:				
means		256±157	209±96	222±118
ranges		20-600	40-480	20-600

The cases can be divided into four groups according to the type of treatment they had (see later): general, cortisone, ACTH and both hormones. The numbers of patients in the four treatment groups and the means of their ages, numbers of comas and doses of insulin are given in Table III. There are no statistically significant differences between any pairs of age means, means of numbers of coma or means of doses. The four treatment groups may, therefore, be compared with each other when the results of treatment are evaluated.

TABLE III

Numbers of patients and means of ages, of numbers of comas and of doses of insulin (units) in the four treatment groups

		Treatment group				
		General	Cortisone	ACTH	Both hormones	All
Numbers of patients	..	7	16	33	6	62
Means:						
Ages	..	29.7	28.7	28.5	30	28.7
Numbers of comas	..	13.1	12.8	11.5	5.7	11.4
Insulin doses	..	267	202	218	251	222

The doses of insulin used were those ordinarily in general use; for example, Thorley and Kay (1951) used a mean dose of 290 units (S.D.156) for men. As is usually found, the mean dose for women was rather less than that for men but not statistically significantly so.

40 per cent. of the cases occurred in the 1st, 2nd, 3rd, 4th or 5th coma the patient had had. Of the men, 47 per cent. had their prolonged coma in the first 5 of their treatment course, as compared with 37 per cent. of the women. This difference is not statistically significant. In the ACTH-treated group, the mean number of comas for the men was 8 and for the women 13 (the difference is not statistically significant). This was because the prolonged coma was the first coma for 4 of the 10 men in this treatment group as compared with only 1 of the 23 women in the same group.

In all, for 5 men and 1 woman their first coma was a prolonged one. This sex difference may be accounted for by the naturally higher dose of insulin required by men and by the possibility that they exhibit a greater resistance to going into coma than women do and so require an exaggerated dose for their first coma (cf. Case (b)).

The relationship of the prolonged coma to the coma treatment course is shown in Figs. 7 and 8. Fig. 7 shows the incidence for both sexes. In Fig. 8 the numbers of prolonged comas are related to successive quintuplet groups of numbers of comas in the treatment courses.

A point of interest is the distribution of the prolonged comas on the days of the week, shown in Fig. 9. Contrary to many opinions, Monday is by no means the day on which most prolonged comas occur. Wednesday holds this dubious distinction. A greater number of cases occur in the second half of the week than in the first half. The small number on Saturday is due to the fact that most hospitals prescribe a rest day on Saturday for their coma patients.

Without added information it is not possible to explain the daily distribution of prolonged comas. It may be, however, that the break in treatment at week-ends allows a recovery of the stressed anterior-pituitary-adrenocortical system which may then call for an increased dose of insulin on Monday. The next two days then intensify the burden on the fatigued defensive mechanisms, leading to a greater number of breakdowns at the middle of the week.

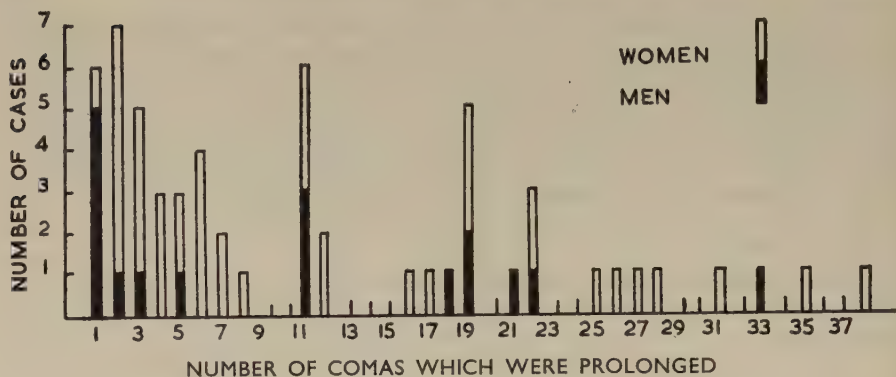


FIG. 7.—Relation of prolonged coma to treatment course. (59 cases.)

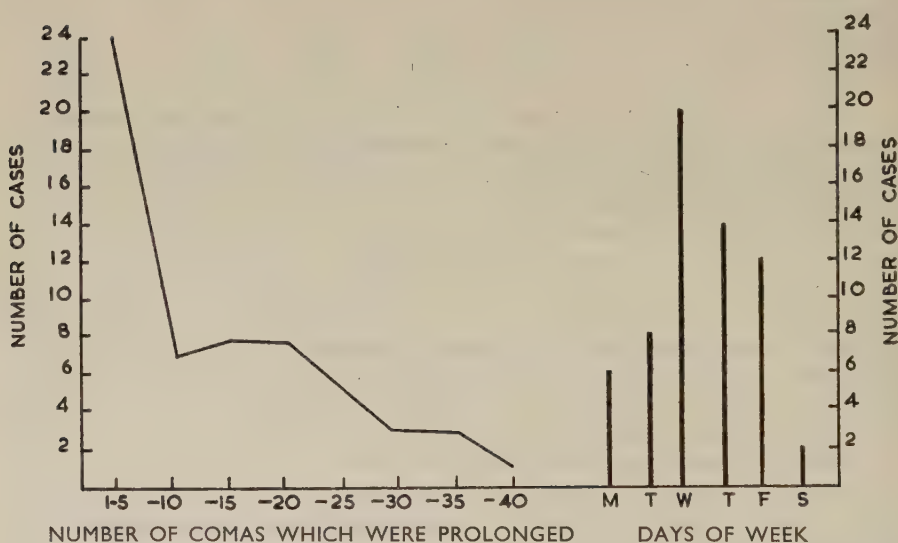


FIG. 8.—Relation of prolonged coma to coma course. (59 cases.) (Kay, 1958.)

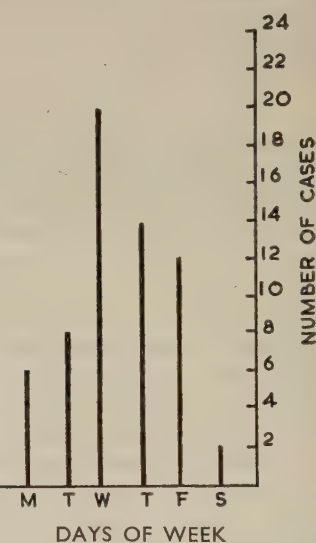


FIG. 9.—Days on which prolonged comas occurred.

Treatment

(1) *General observations.* It is necessary to keep in mind the four types of cases previously discussed. My first approach to the problem of treatment was along the lines of the part played by the gradually growing deficiency of B-vitamins, which are essential for the co-enzymes required for glucose metabolism. One case (Case 1) responded spectacularly to the intravenous administration of a mixture of the principal B-vitamins. Subsequent cases, however, soon indicated the limitations of this form of treatment. Moreover, more use was being made of B-vitamin supplements for patients undergoing deep insulin coma therapy, and among the first remedial measures used in cases of prolonged coma was the administration of large doses of mixed B-vitamins. It was soon evident that the cases to which I was being called were those in which both glucose administration and B-vitamin medication had failed to bring about recovery.

Of the other types of prolonged coma discussed, one case (Case 6) of type B (intense dehydration) and one case (Case 5) of type C (simple glucose lack) were encountered. They responded respectively to intravenous administration of saline (with glucose) and of 33 per cent. glucose solution. The remaining cases all fall into type D. Dehydration is a frequent feature of prolonged coma, but not necessarily a determinative one, and has to be treated as it occurs.

The 62 cases are divided into four groups according to treatment. Seven cases are included in a "general" group. Four of these were treated symptomatically, three have just been referred to above. None of these seven had either cortisone or ACTH. Sixteen cases were treated with cortisone, thirty-three with ACTH and six with both hormones.

It was advantageous to see cases as early as possible after the establishment of the prolonged coma state, but in many cases several hours had elapsed, and in two cases a whole day, before hormone treatment was applied.

(2) *Method of treatment.* The routine approach to a case was to obtain the history of the coma leading up to the prolonged coma, a brief history of the previous comas and recovery therefrom, and an account of treatment given since the first attempted interruption. Note was taken of the amount of glucose given intravenously and of whether gastric stasis had been shown to be present by withdrawing fluid previously given by gavage. An assessment of the clinical state of the patient was next made, especially in regard to depth of coma, circulatory and respiratory state, dehydration and reactivity to stimuli such as supra-orbital pressure. Blood was taken by venepuncture for laboratory investigations and serial capillary blood sugar estimations started, if not already being done.

Treatment was then decided on in accordance with the guiding principles previously stated. General treatment, such as raising the foot of the bed, providing warmth (if necessary) in the form of hot water bottles or electric blanket, was instituted at once. Mixed B-vitamins (thiamine, riboflavin, nicotinamide, pantothenic acid and pyridoxine) were given parenterally if not already administered, and measures taken that appeared obviously necessary to correct dehydration or hypoglycaemia, if established by blood-glucose estimation. If there was still no indication of recovery, hormone was then given by intramuscular injection (55 of the 62 cases). At first, since the effect of neither cortisone nor ACTH was known, doses of 25 mg. were used; later attempts were made to vary the dose according to the insulin dose (hormone dose range 25–100 mg.), but this did not appear to help. Eventually, 50 mg. of either cortisone or ACTH was accepted as a useful first dose, to be repeated an hour or so later if the patient had not recovered. In 6 cases ACTH was given first and followed after an interval by cortisone, especially as the latter was thought to have a better stabilizing effect on the blood-glucose level.

In cases where there was not a prompt recovery after hormone or other treatment, steps were taken to correct any abnormalities in blood chemistry revealed by laboratory tests. Adjustments were required chiefly to plasma bicarbonate and potassium and blood glucose. Correction for the first two was attempted by intragastric feeding, but sodium lactate and potassium chloride were given intravenously when necessary.

Low blood-glucose values were corrected by giving $33\frac{1}{3}$ per cent. glucose in normal saline intravenously. The aim was to maintain the blood glucose in the range 100–300 mg./100 ml. The use of normal saline for intravenous infusion tended to raise the plasma sodium chloride. This rarely passed into dangerous levels, but if it did, correction was made by using weaker saline.

An intra-gastric tube was passed, usually intranasally, and the stomach emptied. A feed consisting of glucose in water was introduced into the stomach. With experience of treating a number of cases, the following formula was adopted as a routine feed:

Water		10 oz. (300 ml.) (half-pint)
Glucose		2 oz. (50 g.) (4 tablespoonsful)
Sodium bicarbonate		60 grains (4 g.) (1 teaspoonful)
Potassium chloride		30 grains (2 g.) ($\frac{1}{2}$ teaspoonful)

The intragastric tube was usually kept *in situ*. Two hours after the first feed, the contents of the stomach were withdrawn and measured. Loss of volume usually meant that the stomach movements were beginning again. The removed feed was replaced by a fresh one of the same composition. This two-hourly change of gastric contents was maintained till the patient was capable of drinking. The potassium chloride was omitted from feeds if the plasma potassium warranted this.

There was no need to give feeds containing other nutrients than glucose until it was certain that recovery would be delayed beyond 24 hours. Even then the chances of vomiting had to be taken into account. In such extended comas, fluid diet with a prepared milk (citrated or pre-digested) basis and necessary salts and accessory factors was started and given by the intragastric tube. Ordinary milk is an abomination because of its clotting. The proneness to vomiting, especially early in the prolonged coma, makes milk clots a lethal menace. If inspired, clots seem invariably to initiate pneumonia.

Nikethamide, strychnine, oxygen and the usual resuscitatory measures were kept immediately available in case of a sudden respiratory and/or circulatory collapse.

(3) *Laboratory investigations.* If not already instituted, on my arrival serial blood-sugar estimations at approximately hourly intervals were started at once. In view of the known effects of insulin coma and of both hormones on the blood chemistry, especially on the electrolytes sodium, potassium, chloride and bicarbonate, appropriate investigations were started at once, blood samples being collected before treatment started and at intervals after. Usually a final check was made after recovery. The essential estimations were those indicated above, blood sugar and plasma electrolytes, to which were added serum total proteins, a full blood count including haemoglobin and packed cell volume as a basis for controlling dehydration and blood volume changes. It was not possible in all cases to do all these estimations; in one or two cases it was impossible to take venous blood.

Further investigations were carried out at leisure to obtain added information about the changes in the blood in prolonged coma.

All the methods used were those ordinarily in use in my laboratory. They were as follows:

Serum:	normal range
bicarbonate	25-35 mN
chloride	95-105 mN
potassium	3.6-5.1 mN
sodium	135-150 mN
proteins: total	5.9-7.5 g./100 ml.
albumin	3.6-7.5 g./100 ml.
globulin	1.8-2.8 g./100 ml.
a/g	1.5-2.3/1

van Slyke (1922).

Whitehorn (1921).

by flame photometer.

by flame photometer.

modified biuret method; albumen-globulin separation by 27.8 per cent. ammonium sulphate adjusted to pH 6.5-7.0. electrophoresis in Antweiler micro-Tiselius apparatus.

inorganic phosphate	0.6-1.6 mN	Kuttner and Lichtenstein (1930).
uric acid	2-4.5 mg./100 ml.	Brown (1945).
cholesterol: total	150-250 mg./100 ml.	Sperry and Webb (1950).
free	40-80 mg./100 ml.	
ester	100-180 mg./100 ml.	
f/e	1/2.0-3.0	
Blood:		
urea	15-40 mg./100 ml.	Archer and Robb (1925).
glucose	70-120 mg./100 ml.	various (Folin and Wu (1920). Hagedorn and Jensen (1941). Nelson (1944)).
cholinesterase	over 45 units	manometric at 30°.
coccarboxylase and thiamine	5-12 µg./100 ml.	Kay and Murfitt (1956).
glutathione	24-37 mg./100 ml.	Kay and Murfitt (1960).
pyruvate	0.5-1.2 mg./100 ml.	Friedemann and Haugen (1943).
lactate	5-20 mg./100 ml.	Barker and Summerson (1941).
Urine:		
steroids (men)	9-19 mg./24 hrs.	Paterson, McPhee and Greenwood
(women)	5-13 mg./24 hrs.	(1942) modified.
	(Note: mN =mEq/lit.)	

In order to be able to do the emergency estimations it was necessary to assemble and take the requisite special laboratory equipment and to take members of my technical staff to supplement the laboratory staff at the hospital where the case of prolonged coma was located. It is not inappropriate at this point to acknowledge the great help given by biochemists and laboratory technicians, often in prolonged spells of work after normal working hours, sometimes throughout the night and always under the stress and drive of an exacting emergency.

IV. RESULTS AND THEIR EVALUATION

Results

These are classified according to the time taken for a full recovery, that is, when the patient was again in touch with his surroundings and able to drink eat and speak. The times are defined as follows:

- Recovery Group 1 prompt—recovery in less than one hour;
2 hours—recovery after one hour, but on same day as the coma started;
3 next day—recovery by the day following the coma, usually, by next morning;
4 days—recovery after the next day but in less than a week;
5 weeks—recovery after more than a week;
6 death.

The results, in gross form, and grouped according to method of treatment, are given in Table 4.

TABLE IV
Results of treatment in the 4 treatment groups
Numbers of cases in recovery group No.

Treatment group	Total cases	1 Prompt	2 Hours	3 Next day	4 Days	5 Weeks	6 Death
General ..	7	2	1	1	—	3	—
Cortisone ..	16	5	3	4	3	1	—
ACTH ..	33	7	6	13	3	2	2
Both hormones ..	6	—	1	1	2	—	2
Totals ..	62	14	11	19	8	6	4

(1) The general treatment group. The three cases that recovered promptly and within two hours were exceptional and were not duplicated in the rest of the series. They belonged to types A, B and C.

Type A. Case 1. 4.5.51. Male aged 28. Nearing end of coma course. Insulin dose 230 units (reduced from 250 units on previous day). At 10.25 a.m., after 30 minutes of coma he was given 180 ml. of 33½ per cent. glucose in saline intravenously. There was partial recovery followed by relapse into coma. A further intravenous infusion of 500 ml. of 33½ per cent. glucose was given at 11.0 a.m., followed by 50 mg. nicotinic acid i.v. at 11.30 a.m. and an intragastric feed of 100 g. glucose and 2 g. of potassium chloride in water. The patient did not recover but remained quiet in coma. Further glucose, 1 pint of 5 per cent. glucose saline and 100 mg. nicotinic acid were given i.v. at 1.35 p.m. with intramuscular atropine and penicillin. I saw this patient at 3.0 p.m. He was then in coma and had been restless but his physical condition was well maintained. The blood glucose was 165 mg./100 ml. Two doses of 10 mg. of thiamine given intravenously at 25 minute intervals were followed by lightening of the coma and rapid progress to recovery within an hour. Next day the patient was well, but complained of paraesthesia, tingling fingers and feet and said that he had had these for some days before the prolonged coma. Treatment with mixed B-vitamins was continued with full recovery from these in about a week. The patient felt well enough to decline further coma treatment.

The blood chemistry is reported in full in the Appendix. The significant abnormalities at 3.0 p.m. on the day of the prolonged coma were:

Plasma bicarbonate	21 mN (m.Eq./litre)
Blood pyruvate	2.5 mg./100 ml.
Blood lactate	60 mg./100 ml.

There was moderate loss of plasma bicarbonate but not enough to cause serious embarrassment of the patient. The blood glucose had been well maintained. The blood pyruvate was high enough to indicate a deficiency of cocarboxylase. (In order to obtain definite evidence about blood cocarboxylase, a method (Kay and Murfitt, 1956) was being developed but was not available for this case.) The fact that this patient did not recover with nicotinic acid injections indicates that B-vitamin deficiency is not confined to a single vitamin. There were no clinical signs of pellagra in this case, the main signs present being referable to thiamine deficiency. The increase in blood lactate was probably due to some restlessness just before the blood sample was taken.

The other case of prompt recovery was a case of simple glucose lack.

Type C. Case 5. 5.5.52. Male aged 21. 21st coma. Insulin dose 350 units. 15 minute coma interrupted by 125 ml. 33½ per cent. glucose i.v. (usually he required about 225 ml. of 33½ per cent. glucose to get him fully round). He awoke promptly but was stubborn and uncooperative. He refused breakfast, vomited his dinner and insisted on taking a bath. He then relapsed into coma. Further intravenous glucose was given i.v., 250 ml. 33½ per cent., followed by his regaining consciousness promptly, only to become comatose again. About 4.0 p.m. he was physically distressed, with temperature 102°, pulse 140/min. and respirations 48/min. I saw this man about 4.30 p.m. On the history, a probable diagnosis of glucose lack was made. The blood glucose was then 45 mg./100 ml. A further 200 ml. 33½ per cent. glucose i.v. brought him out of coma at once. Thereafter, his condition was well maintained and he ate a "breakfast" and later a full supper. The temperature and pulse and respiratory rates returned to normal. This patient had an acute respiratory infection with cough and blood-stained sputum. A streptococcus viridans was isolated. Infections of this type upset insulin mechanisms and maybe this had played a part in this case. The infection cleared up rapidly with penicillin treatment.

The case recovering in 2 hours was one of dehydration.

Type B. Case 6. 10.9.52. Female aged 22. 22nd coma. Insulin dose 260 units. Earlier in the course, she had required 320 units for coma. This had been gradually reduced to 260 units: (mild degree of sensitization to insulin). She had had several difficult recoveries from coma. After 15 minutes' coma, an intragastric feed of 10 oz. strong glucose solution was followed by partial recovery. An hour later the residue of the interrupting feed was withdrawn from the stomach and 225 ml. of 33½ per cent. glucose given i.v. This raised the blood glucose to 300 mg./100 ml. which thereafter was maintained, only falling slowly to 139 mg./100 ml. at 4.30 p.m. Mixed B-vitamins were given and a fresh intragastric feed given at 5.50 p.m. At 5.15 p.m. 44 oz.

of urine had been withdrawn by catheter. I saw this patient shortly after 6.0 p.m. She was very dehydrated, restless and rather exhausted. In view of the steady blood-glucose level this case was assessed as suffering mainly from dehydration. 700 ml. 5 per cent. glucose-saline, 300 ml. normal saline and 200 ml. 33 $\frac{1}{3}$ per cent. glucose-saline given rapidly i.v. were followed by prompt partial recovery and in 2 hours by full recovery. The blood sugar remained high, the last reading at 11.0 p.m. being 260 mg./100 ml.

In this case there was no prolonged hypoglycaemia following interruption and although the blood glucose was well maintained and adequate glucose was given, there was no permanent recovery until adequate fluid was given i.v. to correct the dehydration.

The patient who did not recover till next day was misjudged clinically.

Type D. Case 17. 21.3.53. Female aged 27. 4th coma. Insulin dose 400 units i.v. Her coma had been interrupted by 300 ml. 33 $\frac{1}{3}$ per cent. glucose given i.v., which produced partial recovery followed by relapse into coma. Glucose solution was given intragastrically without effect, followed by further glucose i.v. When first seen, at 5.0 p.m., the patient's blood sugar was 305 mg./100 ml., her general condition was good, there was some dehydration, and she responded purposefully to stimuli. It was felt that cortisone or ACTH would not help. (In the light of fuller experience, this decision is felt to be wrong.) A nasal tube was passed to explore the stomach contents. This evoked much struggling and aroused the patient. The last previous fluid put into the stomach was entirely withdrawn (evidence of gastric stasis), and a fresh feed of water (10 oz.), glucose (100 g.), potassium chloride (2 g.) and sodium bicarbonate (8 g.) given. Withdrawal of the nasal tube produced further stimulation and lightening of coma and the patient appeared to have almost recovered and was able to sit up and drink. As an attempt to complete awaking, 10 mg. of methedrine were given i.v. and repeated in about half an hour. This produced only slight advancement. The blood sugar fell to 45 mg./100 ml. at 8.0 p.m. and intravenous glucose was given. Gastric movements returned and the patient was maintained throughout the night by intragastric glucose with potassium chloride and sodium bicarbonate. Next morning she had recovered. To some extent, this case serves as a control to the hormone treated cases. It is highly probable that either cortisone or ACTH would have produced a prompt recovery, as there was no undue prolongation of the therapeutic hypoglycaemia, interruption having been first attempted by intravenous glucose.

The remaining three cases were treated on general lines; administration of glucose, intravenously and intragastrically, to maintain the blood-sugar level, and of saline, potassium chloride and sodium bicarbonate as indicated by blood analyses. Two were encountered before ACTH and cortisone were available.

One (Case 2. March 1952. Male aged 24. 19th coma. Insulin dose 120 units) was in coma for 3-4 weeks and the second (Case 3. April 1952. Female aged 23. 2nd coma. Insulin dose 280 units) 2-3 weeks. For early blood-glucose values see Figs. 1 and 2. The experience gained in these two cases was valuable in learning the management of long term comas. Observation of the fluctuating glycaemia that occurred led to the conclusion that ACTH or cortisone might help if used early in treatment.

The third (Case 26. September 1953. Female aged 39. 11th coma. Insulin dose 230 units) of these cases was not seen until she had been in coma for over 24 hours. The blood glucose was relatively stable and it seemed unlikely that either ACTH or cortisone would help. Routine general treatment was instituted and the patient recovered in the third week of coma. In all these three cases, the primary interruption was by intragastric glucose, followed by intravenous glucose when recovery did not occur. As a result, the period of hypoglycaemia was prolonged by 80, 70 and 65 minutes respectively, beyond the usual treatment period. For blood chemistry of Case 3 see Appendix.

In this group, then, there were one case of prolonged coma associated with B-vitamin deficiency (Type A), one of simple glucose deficiency (Type C) and one of dehydration (Type B). In none of these was the period of hypoglycaemia longer than was intended for therapy and recovery was quick in response to treatment. The other four cases were of Type D, fluctuating glycaemia. One, having a therapeutic period of hypoglycaemia only, recovered by the next day; recovery could probably have been hastened by cortisone or ACTH. The remaining three cases had hypoglycaemia prolonged far beyond the therapeutic period and recovered only after 2-4 weeks. All the other cases treated fell into Type D and received hormone treatment.

(2) The cortisone treated group. Sixteen cases were treated with cortisone, 8 of whom recovered quickly, 5 in less than one hour and 3 within a few hours. Four of the remaining 8 recovered by the next day, and 4 after longer periods. Typical cases will be described.

Prompt recovery. Case 4. 1st May, 1952. (The first case treated with hormone.) Male, aged 28. 33rd coma. Insulin dose 380 units. Nothing abnormal was noted during the coma. After 25 minutes' deep coma, 250 ml. of 33½ per cent. glucose in saline were given i.v. to interrupt the coma but did not rouse the patient. One pint of 40 per cent. glucose was given intragastrically, still without effect. The patient became very distressed and was given nikethamide and adrenalin by injection and oxygen by inhalation. One and a half hours after the attempted interruption there was slow recovery and the patient was able to sit up in bed but began to relapse into coma. Further glucose, 5 per cent. solution in saline, was given i.v. When I saw this patient at 4.0 p.m., five hours after the first attempted interruption of coma, the patient was comatose and gradually slipping back into deep coma. Blood chemistry is given in the Appendix. He had had 96 g. of glucose i.v. and 200 g. intragastrically. His general condition was good, blood sugar was 65 mg./100 ml. and electrolytes normal. B-vitamins (as Becosym) were given intramuscularly without effect. The blood pyruvate was normal at this time. The stomach was empty, acid was present, enabling 20 oz. of 40 per cent. glucose solution to be given intragastrically. As there were no signs of recovery, 25 mg. of cortisone were given intramuscularly, the time being 5½ hours after the first attempt at interruption. There was a rapid lightening of the coma and in 10 minutes the patient was able to sit up and drink. He was still drowsy, but rousable and soon able to speak in a confused manner. He continued to make good progress, his blood sugar increased and was maintained and in due course he was able to eat a normal supper. This patient had a blood uric acid of 13.6 mg./100 ml. (? evidence of nuclear damage) which slowly fell. The day following coma, the white blood cell count was 16,500/cu.mm. (75 per cent. polymorphs). His ketosteroid excretion was just subnormal (8.4 mg./24 hrs.) the day after his prolonged coma, suggesting poor adrenocortical function. A week later it had risen to 12.7 mg./24 hrs. For blood chemistry see Appendix.

Recovery in hours. Case 12. 16.12.52. Female, aged 34. 4th coma. Insulin dose 40 units. Uneventful coma. After 20 minutes' deep coma, 100 ml. of 33½ per cent. glucose in saline given i.v. failed to rouse the patient. A further 80 ml. were given at once. There was slight lightening of the coma followed by a deepening. A further 180 ml. of 33½ per cent. glucose solution given i.v. with mixed B-vitamins (Becosym) produced lightening of the coma with much restlessness. This was the state of the patient when seen by me 90 minutes after the first attempted interruption. The blood electrolytes were normal and the blood sugar 70 mg./100 ml. Cortisone, 25 mg. given intramuscularly produced a rapid response. Ten minutes after the cortisone the patient opened her eyes and appeared to be rousing. After a further ten minutes she was able to drink freely but was not progressing as quickly as was desired. Three hours after the first attempt at interruption a second dose of 25 mg. of cortisone was given i.m. At this point the blood electrolytes were still normal and the blood glucose was 83 mg./100 ml. Progress was now steady, the patient taking glucose drinks freely. After a short period of hysterical weeping, the patient roused herself into a sitting position and appeared to be fully roused about 2½ hours after the first dose of cortisone. The blood sugar was then 115 mg./100 ml. When first seen, this patient had a blood pyruvate of 1.8 mg./100 ml., a value which suggested that there was some thiamine deficiency. She also had a low 17-ketosteroid excretion, 2.4 mg./24 hrs. on the day following the prolonged coma. For blood chemistry see Appendix.

Recovery by next day. Case 16. 25.2.53. Female, aged 28. 2nd coma. Insulin dose 250 units. Uneventful coma. After 10 minutes' deep coma, interruption was attempted by intragastric administration of 50 g. of glucose in 8 oz. of water. There was no response to this, and 400 ml. of 33½ per cent. glucose in saline with 2 ml. of nikethamide were given i.v. 80 minutes after the onset of deep coma, without effect. An intragastric tube was passed 2 hours and 40 minutes after the first attempt at interruption by intragastric feed, and the whole of this feed was withdrawn and replaced by a similar fresh one. Three hours later 500 ml. of 33½ per cent. glucose in saline with nikethamide and Becosym were given i.v. I first saw the patient about 6 hours after the onset of deep coma. The patient as still in moderately deep coma and in good physical condition. Blood was taken for chemical estimations and 50 mg. of cortisone given i.m. The blood sugar just before this was reported to be 394 mg./100 ml. Twenty minutes after the cortisone the patient was recovering and could be roused by slapping and calling to her. She sat up and was able to drink with difficulty, but remained somnolent and tended to go to sleep again. The blood glucose was being maintained, the value being 348 mg./100 ml. one hour after the first test. In view of the marked somnolence, 20 mg. of Methedrine were given i.v. Instead of waking the patient, the Methedrine evoked uncontrolled violent motor activity which lasted for about half an hour. At this point the plasma bicarbonate (sample taken just before giving the cortisone) was reported to be 14.5 mN, the other electrolytes being normal. Bicarbonate of soda, 8 g. in solution, was given by gavage to correct the acidemia. This appeared to be absorbed rapidly, for in about a quarter of an hour the plasma bicarbonate had

risen to 23 mN. By this time (about 8½ hours after the onset of deep coma) the patient's condition appeared to be stabilized, but she had not fully recovered and was still restless. Glucose was given by gavage, but the blood glucose slowly fell and a further intravenous infusion of 450 ml. of 33½ per cent. glucose in saline had to be given. Gardenal gr. iv. was given as a sedative. Glucose drinks were given at intervals during the night. By morning the patient was rousable, able to speak when addressed and by mid-day was fully awake, in good condition, but with a "hangover".

Recovery after a few days. Case 59. 17.8.55. Female, aged 36. Habitually slow in recovering from coma. 12th coma. Insulin dose 260 units. Uneventful coma. After gavage, the coma lightened for a time, then suddenly the patient relapsed into deep coma. Intravenous infusion of 25 ml. of 33½ per cent. glucose in saline, given with difficulty 45 minutes after gavage, had little effect. Later larger amounts failed to rouse the patient, although the blood glucose was raised to 300 mg./100 ml. When seen by me about 5 hours after the first attempted interruption, the patient was in moderately deep coma. The plasma sodium, potassium and chloride were normal, but the bicarbonate was low, 19 mN. Cortisone, 50 mg., was given i.m., followed by lightening of the coma and partial rousing of the patient, so that she was able to drink a little. The blood glucose appeared to be stabilized at 120 mg./100 ml. Emptying of the stomach by intra-nasal tube showed that little, if any, of the feed given to interrupt coma had been absorbed. A fresh feed, 10 oz. of water, 30 g. of glucose, 4 g. of sodium bicarbonate and 2 g. of potassium chloride, was introduced into the stomach. As the patient appeared to be nearly roused but not making progress, 30 mg. of Methedrine were given i.v. This produced violent, purposeless physical activity lasting 30–35 minutes, but no restoration of mental activity. Withdrawal of stomach contents showed that there was still gastric stasis, and it was decided to give 100 ml. of 33½ per cent. glucose in saline i.v. with 35 ml. of 50 per cent. sodium lactate to raise the plasma bicarbonate. This was followed by a second 50 mg. of cortisone given i.m. Stable blood-glucose values were by this time attained, but the patient was still not rousable. A regime of two-hourly intragastric feeds, the same as the last previously given, was arranged, with intravenous glucose infusions as indicated by the blood glucose values or the state of the patient, and a course of penicillin (Estopen) started. The blood glucose was well maintained throughout the night and the patient slowly progressed. On the second day, however, her blood pressure fell to 90 mm. Hg. systolic and 70 mm. Hg. diastolic. As the plasma chlorides fell to 88 mN and the plasma potassium rose to 5.1 mN, the asthenia of this period was probably due to renewed temporary adrenocortical failure. At this stage, further cortisone would probably have helped. Instead, sodium chloride was added to and potassium chloride omitted from the i.g. (intragastric) feeds, as fluids were now being passed on by the stomach. The regime of i.g. feeds described was continued and by the end of the day the systolic blood pressure had risen to 120 mm. Hg. and the patient was progressing towards recovery. By the middle of the next (third) day, she was able to speak and drink and pass urine normally. Complete recovery was not attained until the fifth day. For blood chemistry, see Appendix.

Recovery after weeks. It is not necessary to describe any of these cases in detail, as their early course closely resembled that of Case 59. There are, however, two additional requirements (a) to continue the prophylactic use of penicillin, and (b) to arrange a fluid diet adequate in composition and caloric value to maintain strength. The basis of this is milk, reinforced by dried or concentrated milk or milk preparations, with added glucose, salts and vitamins, and made up to 3–4 litres with water. In the early days, when there is a danger of vomiting, citrated milk, or milk preparations that do not clot, should be used. A fluid balance chart should be kept. Treatment is directed to maintaining the patient in good physical condition to enable restoration of cerebral cortical function to occur naturally. The blood chemistry should be checked daily at first and then less frequently as normal values are maintained.

(3) ACTH-treatment group.

(4) "Both hormones" treatment group. Only one illustrative case from these groups will be quoted, as the principles of treatment are the same as those indicated in the cortisone treatment group. The cases in the "both hormones" treatment group may be regarded as failures or partial failures of ACTH treatment, since in all six cases ACTH was given first and cortisone later.

ACTH-treatment group. Case 13. 17.12.52. Female (Indian), aged 28. Rather undernourished. 3rd coma. Insulin dose 190 units. Uneventful coma. Intravenous glucose-saline, 170 ml. of 33½ per cent. glucose, given after 15 minutes' deep coma, failed to rouse the patient. Further infusions to a total of 700 ml. of 33½ per cent. glucose-saline, had little effect. There was slight lightening after administration of Becosym. When first seen by me 1½ hours after the first attempt at interruption, the patient was still in deep sopor and could not be roused. The blood glucose was 605 mg./100 ml. and the plasma bicarbonate 20.5 mN; the other electrolytes were in normal concentration but the pyruvate was raised, 1.7 mg./100 ml. ACTH, 25 mg., was given i.m. For almost ten minutes the patient lay prone without apparent change

in her condition. Then suddenly she turned over in bed, sat up and appeared fully awake. She drank readily and in a few minutes was in full touch with her surroundings and able to speak. Very shortly she was able to take a light meal. This recovery, if it had occurred as the result of a normal i.v. interruption, would have been accepted as a normal recovery. This patient's ketosteroid excretion in the 24 hours following recovery was 8.5 mg., a low value since it included the steroids produced in response to the ACTH.

Evaluation of results and of treatments

(1) Comparison of results of hormone treatment with those when hormone was not used. One of the difficulties in evaluating the results here presented is the absence of adequate controls. In investigating a form of treatment of prolonged insulin coma, it is not possible to omit the treatment from alternate cases, as can be done in some other therapeutic trials, because there is no adequate alternative form of treatment and each case is potentially fatal. If the experimental method offers a hope of success or is found to work, every patient must have the advantage of receiving it. Furthermore, cases vary so much between themselves that selection of alternate cases for treatment would not necessarily give comparable series. The three special cases in the "general" treatment group illustrate this. They are different in character from all the others and do not form a strict control group for all the others.

On the other hand, the other four cases in the "general" treatment group do form a small control group for the 55 hormone-treated cases. As has been pointed out, Case 17, which recovered by the second day, would probably have recovered in a few hours or even less after hormone had this been used. The remaining three cases recovered only in 2-4 weeks. These contrast markedly with the 55 hormone-treated cases, 40 of which recovered by next day or earlier and only 3 failed to recover until the 3rd or 4th weeks (excluding the 4 deaths).

Taking Table IV as it stands, there is no statistically significant difference between the results from the four treatment groups, the distribution being therefore within the range of chance. It may be reasonably argued, however, that since the 55 hormone-treated cases had had adequate "general" treatment and failed to recover within "hours" after the first attempt to interrupt their coma and there was usually some interval before hormone was given, to make sure that the patient was not recovering, they form a control series for comparison with hormone treatment. Table IV could then be revised to give Table V. According to this table 5 per cent. of the control cases recovered in "hours" or less, as compared with 40 per cent. in the hormone treated series. It scarcely needs a statistical test to establish the significance of this difference between the series. (When tested by the χ^2 test P is <0.001 .)

TABLE V

Distribution of results of treatment using the 55 hormone-treated cases as failed general treated cases., i.e. as controls for the hormone-treated cases

Series	Form of Treatment	Recovery Group		Total
		1-2	3-6	
Control	General	3	4	7
	General followed by hormone	—	55	55
	Total	3	59	62
		(5 per cent.)		
Experimental ..	Hormone	22	33	55
		(40 per cent.)		
Both		25	92	117

Except that the cases which recovered early tended to have shorter periods of hypoglycaemia than those that recovered after days or weeks, there was no clinically apparent difference between the cases.

(2) Relation of results of treatment to dose of insulin used to induce coma. The means of the doses of insulin for the sex and treatment groups have been given in Tables II and III. The means of the doses of insulin used in the cases in the various treatment and recovery groups are given in Table VI. The only significant difference between means is that the mean of the doses of cases in recovery group 2, 179 units, is significantly lower than 308, the mean of the doses in group 4 ($P < .05, > .02$). There seems to be no rational explanation for this finding. There is no significant overall correlation between mean dosage and types of recovery and between dosage and numbers of comas patients had had. There is no significant difference between the mean dosages of those who recovered quickly (groups 1 and 2) and of those who recovered less easily (groups 3-6) in the cortisone and ACTH treatment groups or between the mean dosages of those who recovered well (groups 1 and 2) in these two treatment groups, or between the mean dosages of those who recovered less easily in these two treatment groups.

TABLE VI

Means of doses (units) of insulin used to induce the comas in the various recovery and treatment groups

Recovery Groups			Treatment Groups			
			General	Cortisone	ACTH	Both Hormones
1.	Prompt	..	290	226	214	—
2.	In hours	..	260	153	178	180
3.	Next day	..	400	175	216	120
4.	Days	..	—	243	310	400
5.	Weeks	..	210	180	250	—
6.	Death	..	—	—	208	205
All			267	200	218	252
						222

If the deaths (cases in recovery group 6) are excluded from the ACTH-treated cases, the correlation between mean dosage and type of recovery in the ACTH-treated cases becomes almost statistically significant (P slightly > 0.05), the tendency being for patients who had the lower doses of insulin to recover most easily from their prolonged coma.

On the whole, however, the dose of insulin can be said not to have determined the type of recovery. This is to be expected, since the coma-producing dose is personal to each patient and reflects his reaction to the treatment as conditioned by his endocrine status and his mental resistance to or acquiescence in coma. It will be seen later that the factor determining the type of recovery is the length of the extra period of hypoglycaemia.

(3) Relation between numbers of comas patients had had and type of recovery. In Table VII, the means of the numbers of comas patients had had are analysed in relation to form of treatment and type of recovery. There is an obvious tendency for the patients who recovered quickest (recovery group 1) to have had the greatest number of comas. The mean number of comas of patients in recovery group 1 (21.6) is not determined by the route of primary interruption and is statistically significantly greater than the mean number of comas of

patients in each of the other five recovery groups, which latter do not differ significantly among themselves.

TABLE VII

Relation between mean numbers of comas patients had had (including the prolonged one) to form of treatment and type of recovery

Treatment Groups	Means of numbers of comas in recovery groups						All
	1	2	3	4	5	6	
General	21	22	4	—	10.7	—	13.1
Cortisone	29.3	7.7	5	8.3	7	—	12.8
ACTH	16.7	12.5	9.7	5.7	4.5	21	11.5
Both hormones ..	—	2	2	12	—	3	5.7
All	21.6	11.1	8	8.3	8	12	11.4

Although there is no significant overall correlation between means of numbers of comas and types of recovery, yet if deaths are excluded, the correlation between means of numbers of comas and type of recovery becomes significant for the ACTH-treated cases and the cases as a whole. If the cases are grouped according to the numbers of comas they had had (1-5, 6-15, and over 15 comas) and into two main recovery groups (good: groups 1 and 2; not so good: groups 3-6) Table VIII can be constructed. Although the distribution of cases in this table is not quite statistically significant, there is an obvious tendency for cases who had had most comas to recover quickest from prolonged coma and for those who had had fewest comas to recover less easily.

TABLE VIII

Numbers of cases in recovery groups related to numbers of comas they had had

Numbers of Comas	Numbers of cases in recovery groups		Total (100%)
	1-2	3-6	
1-5	6 25%	18 75%	24
6-15	4 27%	11 73%	15
15-38	12 60%	8 40%	20
All	22 40%	37 60%	59

The probable explanation of this tendency and for the high mean number of comas in recovery group 1, is that insulin dosage was better stabilized and the pattern of return to consciousness better known in those patients who were most advanced in their treatment course than in those who had had fewer comas. In other words, relative over-dosage with insulin is easier and more probable and failure to awake more difficult to recognize during the earlier comas than in the later ones when doctors have had longer opportunities of observing patients' reactions and patients had become better adjusted to the type of treatment. This links up with the incidence of prolonged comas in relation to the treatment course (see Figs. 7 and 8). The greatest number of prolonged comas occurred in those cases where the dose was most recently arrived at and the patient's adaptation to and acceptance of the coma process and recovery had not fully developed.

It is worth relating these facts to the evidence of the state of the adrenal function in patients undergoing insulin coma treatment (as examples, see Figs. 3, 4 and 5). Many patients enter upon their coma course with their

anterior-pituitary-adrenocortical system already fatigued (cf. Figs. 4 and 5) by the stress of their illness. This fatigue is aggravated by the new stresses of the dosage building-up period before the first coma. These are potential cases for the prolonged comas that occur early in the treatment course. As the coma course proceeds, there is first, stimulation or depression and later, fatigue of the anterior-pituitary-adrenocortical system, with fluctuations in the functioning state, depending on the reserve reactivity of the system. During the periods of depressed function, the prolonged comas in the later part of the treatment course occur. Note the increase in the numbers of prolonged coma about the 11th and 19th-22nd comas (Fig. 7).

The relation of the incidence of prolonged comas to the days of the week is also relevant when considering the effects of the coma stress (see Fig. 9). Statistical analysis shows that the distribution of prolonged comas in Fig. 9 is not due to chance; distribution by chance may be expected to give the same numbers of prolonged comas on each day of the week, except Saturday, since the numbers of comas given on each of the five days, Monday to Friday, can be expected to be the same.

The distribution of types of recovery does not differ significantly on the different days of the week (excluding Saturday with only 2 cases) and there are no significant differences between the means of the number of comas per prolonged coma per patient on the different days of the week. Yet more prolonged comas occur in the middle and later days of the week than in the earlier part. The week-end without comas gives an opportunity for the anterior-pituitary-adrenocortical system to recuperate so that the first coma of the week is well managed by the patient. Thereafter, the accumulating stress of the comas tends to produce breakdown and prolonged comas later in the week. This explains the greater incidence of prolonged comas on Wednesday to Friday. If, however, Wednesday is passed without a prolonged coma, there is a reasonable chance of the patient's completing the week without trouble. The only hospital that gave deep coma treatment on Saturdays provided the third highest number of prolonged comas of all the thirteen hospitals, and of them, the number occurring in the first two days of the week was disproportionately slightly high.

Ten patients with prolonged comas were having their second or third coma course. It seems a reasonable surmise that 10 is a much higher proportion of the number of patients having a second or third coma course than is 52 (the remainder who had a prolonged coma in their first course) of the number of patients having their first course of coma treatment. The mean dose of insulin these patients had was 212 units (mean dose for all 62 patients, 223 units) but their mean number of comas was 5.8, only half the mean number (11.4) for all the 62 prolonged comas. None of these 10 patients had a prompt recovery, three were in recovery group 2 and the rest in groups 3 (4 patients), 4 (1 patient) and 5 (2 patients). The chronic schizophrenic, such as those who have repeated courses of deep insulin coma treatment, is prone to have poor endocrine reactivity at a low level. Therefore, he is likely to react badly to stress. He appears more prone to prolonged comas and does not make as good a recovery from them as does the schizophrenic in an earlier stage of his disease.

From our consideration of the incidence of prolonged coma in relation to the coma treatment course, it is possible to conclude that the stresses in the early part of the course precipitate prolonged comas in those who are just entering upon their series of therapeutic comas and in the later part of the course the stresses precipitate prolonged comas in those whose endocrine defensive mechanisms are becoming fatigued. The weekly fluctuation of stresses mediated

in part by the week-end break in treatment plays a part in shifting the greater incidence of prolonged comas into the middle and second half of the week.

(4) Relation of results of treatment to interval between onset of therapeutic coma and giving of hormone in cases treated with one hormone. In most cases it was possible to calculate the interval between the recorded time of onset of the therapeutic stage of the deep coma and the time of giving hormone. Excluding two cases seen first on the second day of their prolonged coma, the mean intervals for all cases and for the ACTH- and cortisone-treated groups are given, and related to type of recovery, in Table IX. There are no statistically significant differences between any pairs of means and no statistically significant correlation between the intervals before giving hormone and the results of treatment. The small group treated with both hormones shows no difference from the bigger groups.

TABLE IX

Means of periods (in hours) between onset of coma and giving of hormone

Recovery Group					Treatment Group		
					Cortisone	ACTH	Both Hormone
1. Prompt	..	..	..	..	5.0	4.8	4.88
2. In hours	..	..	..	..	3.2	3.8	3.56
3. Next day	..	..	..	..	5.5	4.5	4.75
4. Days	..	..	..	..	4.5	5.3	4.91
5. Weeks	..	..	..	..	4.75	*	—
6. Death	..	..	..	..	—	4.25	4.25
All	..	..	..	..	4.67	4.53	4.58

* Not known

The results of treatment are not determined by the interval elapsing before giving hormone in the ranges of time covered by these cases (1.5–9.25 hours). Cases in recovery group 2 tended to have a shorter time interval before hormone was given, just as they also tended to have lower insulin doses than did other cases.

(5) Effect of duration of hypoglycaemia. The relationship between the extra period of hypoglycaemia and the type of recovery is shown in Table X. Five cases are omitted because the extra period could not be determined. This extra period is measured in minutes elapsing between the first attempt at interruption and the first i.v. administration of glucose. In cases where interruption was by the i.v. method, this "extra period" is nil (0 in Table).

TABLE X

Relation of extra period (minutes) of hypoglycaemia in the treatment groups to type of recovery

Treatment Group				Recovery Group					
				1	2	3	4	5	6
General	range	..	..	0.0	65	0	—	65–80	—
	mean	..	..	0			—	72	—
Cortisone	range	..	..	0–40	0–25	15–70	40–50	25	—
	mean	..	..	8	8	36	45		—
ACTH	range	..	..	0–100	0–40	0–170	0–85	45	55
	mean	..	..	26	21	30	42		
Both Hormones	range	..	..	—	30	20	60	—	95,300
	mean	..	..						
All	mean	..	..	16	22	29	40	57	150

Where means not given, only one case available. Five cases omitted.

Although the groups in the table are too small for full statistical analysis, the figures do show a definite trend: the cases that recovered "promptly" and in "hours" had had shorter extra periods of hypoglycaemia than had those which recovered "next day", later or not at all. This is emphasized if one case which had 100 minutes' extra hypoglycaemia is excluded from the ACTH-treated "prompt" recovery group, the mean for the remaining 7 cases being 13 minutes. The mean duration of the extra hypoglycaemia for the 25 cases in the "prompt" and "hours" recovery groups was 18 minutes; for all the other cases it was 48 minutes. The difference between these means is statistically significant in the range $P < .05 > .02$.

There is a significant correlation between the shortness of the extra period of hypoglycaemia and the type of recovery in the ACTH-treated cases ($\rho = 0.9$) and an almost significant one for the cortisone cases ($\rho = 0.7$). Taking all the cases, there is a complete inverse correlation between type of recovery and mean extra period of hypoglycaemia.

Table X, then, supports the clinical impression that those patients recovered quickest whose failure to awake after primary interruption was detected earliest and who had been given i.v. glucose promptly, i.e. had had the shortest periods of extra hypoglycaemia. This inference is also supported by comparing the rates of recovery according to the method of primary interruption. Of the 19 cases that received i.v. glucose for primary interruption, 13 (68.4 per cent.) recovered on the first day, 5 by the second day and 1 later. Of the 43 cases that received i.g. glucose at the first attempt at interruption, only 12 (27.9 per cent.) recovered on the first day, 14 on the second day, 9 in days or weeks, and 4 died. These results are summarized in Table XI. The distribution of these results is statistically highly significant ($P = < .01 > .001$). Clearly, i.v. administration of glucose to interrupt coma is better than i.g. However, the practical difficulties of its continuous use—poor veins, risk of thrombosing veins and so on—and the fact that glucose can be given i.g. by nurses, account for the more general use of the i.g. route.

TABLE XI
Relation of types of recovery to routes of primary interruption

Route of Primary Interruption	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
Intravenous	13 (68.4%)	6 (31.6%)	19
Intragastric	12 (27.9%)	31* (72.1%)	43
Both	25 (40.3%)	37 (59.7%)	62

* Includes 4 deaths

Since the i.v. route for primary interruption is so much better than the i.g., it is necessary to examine the results of treatment taking into account the method of primary interruption. All the 19 cases that had i.v. primary interruption had "general" treatment; 2 recovered early, 17 did not. These 17 had hormone treatment; 11 recovered early, 6 later. These figures are shown in Table XII.

TABLE XII

Relation of types of recovery to treatment in cases that had intravenous interruption

Treatment	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
General	2 (10.5%)	17 (89.5%)	19
Hormone	11 (64.7%)	6 (35.3%)	17
Both	13 (36.1%)	23 (63.9%)	36

All the 43 cases that had i.g. primary interruption had "general" treatment; 1 case recovered early, 42 did not. Of these 42, 38 had hormone treatment; 11 recovered early, 23 later, and 4 died. These figures are shown in Table XIII.

TABLE XIII

Relation of types of recovery to treatment in cases that had intragastric interruption

Treatment				Recovery Groups		Total (100%)
				1 and 2	3 to 6	
General	..	..	..	1 (2.3%)	42 (97.7%)	43
Hormone	..	..	..	11 (28.9%)	27 (71.1%)	38
Both	..	..	..	12 (14.8%)	69 (85.2%)	81

The distribution of the results in both these tables is statistically highly significant ($P = < .001$). Thus the value of hormone treatment is again established whatever the method of primary interruption.

It is, therefore, possible to conclude that in prolonged comas, i.v. primary interruption gives a better chance of early recovery than does i.g., that the shorter the period of extra hypoglycaemia the better are the results of subsequent treatment, and that over and above these, hormone treatment gives better results than general treatment.

(6) Comparison of results with ACTH and with Cortisone. The method of primary interruption must be taken into account when comparing the results obtained with cortisone with those with ACTH. Of the 8 cortisone-treated cases that recovered on the first day, 6 had had i.v. glucose to interrupt their coma, whereas of the 13 corresponding ACTH-treated cases, only 5 had had i.v. glucose at the normal time of interruption. Against these are to be set 6 ACTH treated cases that had had i.v. glucose at the first attempt at interruption, yet did not recover till the next day or for a few days. The results for the 49 cases treated with a single hormone are analysed in Tables XIV, XV and XVI.

The distribution in Table XIV is probably significant (the value 0 in one box makes testing of doubtful value, but on the figures, $P < .05$, $> .02$), but in Tables XV and XVI the distribution is not better than would be due to chance, ($P < .5$, $> .3$). It seems probable that cortisone could be expected to give better results after primary i.v. interruption than ACTH, but not after primary i.g. interruption. This can be further tested by examining the cases that recovered "promptly" and "in hours" (recovery groups 1 and 2) according to the hormone used and the method of primary interruption. This is done in Table XVII.

TABLE XIV

Results in cases that received intravenous primary interruption and hormone treatment

Treatment				Recovery Groups		Total (100%)
				1 and 2	3 to 6	
Cortisone	..	..	..	6 (100%)	0	6
ACTH	..	..	..	5 (45.5%)	6 (54.5%)	11
Both	..	..	..	11 (64.7%)	6 (35.3%)	17

TABLE XV

Results in cases that received intragastric primary interruption and hormone treatment

Treatment			Recovery Groups		Total (100%)
			1 and 2	3 to 6	
Cortisone	..	..	2 (20%)	8 (80%)	10
ACTH	..	..	8 (36.4%)	14 (63.6%)	22
Both	..	..	10 (31.3%)	22 (68.7%)	32

TABLE XVI

Results in all cases treated with a single hormone

Treatment			Recovery Groups		Total (100%)
			1 and 2	3 to 6	
Cortisone	..	..	8 (50%)	8 (50%)	16
ACTH	..	..	13 (39.4%)	20 (60.6%)	33
Both	..	..	21 (42.8%)	28 (57.2%)	49

TABLE XVII

Relation of route of primary interruption to hormone used in cases that recovered in the first day

Hormone			Route of interruption		Total (100%)
			Intravenous	Intragastric	
Cortisone	..	..	6 (75%)	2 (25%)	8
ACTH	..	..	5 (38.5%)	8 (61.5%)	13
Both	..	..	11 (52.4%)	10 (47.6%)	21

Again the groups are small for statistical analysis, but the distribution is not different from chance ($P < .2$, $> .1$). There is then no evident statistically significant difference between the various combinations of hormone and route of primary interruption, although cortisone seems to give better results than ACTH after i.v. primary interruption. This being so, it is reasonable to act on the inference that cortisone and ACTH appear to give similar results whatever the method of primary interruption. Better results can be expected with either hormone if the primary interruption was by i.v. glucose than if it was by i.g.

(7) Deaths. There were 4 deaths in the series, one from broncho-pneumonia, one from renal failure and two from shock or exhaustion.

Case 18. 24.4.53. Female, aged 23. 5th coma; insulin dose 210 units. Normal coma. Attempted interruption by gavage at 10.45 a.m. was followed by a major fit and the patient made a slow apparent recovery. She vomited her dinner, became shocked and at 3.45 p.m. was in coma again. Intravenous 33½ per cent. glucose at 4.30 p.m. and 6.30 p.m. produced lightening of the coma but not recovery. When I first saw her at 7.30 p.m. she was deeply shocked. ACTH, 100 mg., given by i.m. injection produced lightening of coma followed by attempts to sit up but not full awaking. Methedrine, 10 mg., i.v. was without perceptible effect. Gastric stasis persisted and more glucose was given i.v. and Becosym i.v. At 11.40 p.m., 50 mg. of cortisone was given but without apparent effect and the patient was in a profound collapse. Glucose continued to be given by both routes. On the morning of the 25th, the blood chemistry was as follows: serum sodium 158.7 mN, potassium 10.5 mN, chlorides 121.8 mN, bicarbonate 28 mN, uric acid 18 mg./100 ml., urea 39 mg./100 ml., pyruvate 4.6 mg./100 ml. Allowing for the i.v. saline given, the potassium value suggests adrenal failure. The pyruvate indicates failure of co-enzyme mechanisms, in spite of the B-vitamins given. There was no improvement and she died on the evening of the 25th.

In this case, a major fit provoked a deceptive pseudo-recovery, but the increase in blood glucose that usually follows a fit was apparently not maintained because of the gastric stasis that was responsible for the vomiting. There was a long period (about 5½ hours) of extra hypoglycaemia which was not rectified till late in the afternoon. These conditions were responsible for the collapse in a poorly reactive subject.

Case 33. 4.2.54. Female, aged 30. 26th coma, insulin dose 240 units reduced from 260 units on previous day. Usually recovered easily from coma. After an apparently normal coma of 20 minutes' duration, i.g. glucose failed to produce a response. Glucose, 250 ml. of 33½ per cent., given i.v. 35 minutes after the attempted interruption failed to rouse her. The extra period of hypoglycaemia was thus short. Further 33½ per cent. glucose with Becosyn was given i.v. one hour later without result. Gastric stasis was proved by withdrawing stomach contents. I saw her about 4 hours after the first attempt at interruption. She was then deep in coma, shocked, cyanosed and giving the appearance of acute cardiac failure and breathing deeply as if in acidosis. The blood chemistry results were: plasma sodium 130 mN, potassium 3.3 mN, chloride 115 mN, bicarbonate 17 mN, urea 24 mg./100 ml., uric acid 12.8 mg./100 ml., pyruvate 3.1 mg./100 ml. and cocarboxylase 13.7 µg./100 ml. There was some dehydration with gastric stasis and achlorhydria. ACTH, 50 mg., followed by a second dose of 50 mg. forty minutes later produced lightening and some improvement. Improvement was not maintained although the blood glucose was kept in the range 98-418 mg./100 ml. The patient died on the 6th about 49 hours after the first attempt to interrupt her coma. Shortly before death the blood chemistry was: serum sodium 148 mN, potassium 8.5 mN, chloride 137 mN, bicarbonate 17 mN, urea 96 mg./100 ml., uric acid 8.1 mg./100 ml. and pyruvate 4.6 mg./100 ml. Death was apparently due to exhaustion with some adrenal and cardiac failure and early broncho-pneumonia.

Case 48. 7.10.54. Male, aged 31, of south-east Asian stock. 1st coma, insulin dose 200 units. As this was the patient's first coma, interruption was attempted as soon as deep coma was diagnosed. Intra-gastric glucose produced an apparent recovery and the patient sat up. He shortly relapsed into coma, was given more glucose i.g. without effect as there was gastric stasis, and then 33½ per cent. glucose i.v. with Becosyn 95 minutes after the first attempt at interruption. Methedrine, 30 mg. i.v., was ineffective. I saw this patient about 3 hours after the first i.g. glucose was given. The only abnormalities in the blood chemistry were serum bicarbonate 17 mN and uric acid 8.2 mg./100 ml. The W.B.C. was 18,500/cu.mm. ACTH, 50 mg., followed in ¾ hour by cortisone, 50 mg., produced only slight lightening of coma. Mechothane was given i.g. but did not start gastric movements. There was some respiratory distress. This patient seemed to be completely devoid of that drive that the patient whose coma lightens must exert to recover. His mental illness was characterized by severe depression and an intense desire to die which did not express itself by attempts at suicide. During the following days he remained unconscious, and his blood chemistry changed fairly steadily. On the 4th day (10.10.54) there was haematuria. Cortisone, 25 mg., i.m. on the 12th and 13th was ineffective. The serum sodium rose to a value of 160 mN on 15th October; the bicarbonate rose to 34 mN and then fell to 16.5 mN on the 15th; the inorganic phosphate rose to 4.0 mN, the uric acid to 13.2 mg./100 ml. and the blood urea to 420 mg./100 ml. on the 15th, in the evening of which he died. This was apparently a death from renal failure probably due to the effects of the prolonged coma, associated with a terminal broncho-pneumonia. Renal damage does occur in insulin comas prolonged more than about 48 hours. There was an increase in blood urea in Case 33. Case 2, a man aged 24, whose coma lasted 3-4 weeks, had a moderately severe toxic nephritis in the second week of his coma, with albumen, granular casts and red blood cells in the urine, blood urea 91 mg./100 ml. and raised diastolic blood pressure. As this nephritic episode subsided, he gradually improved.

Case 50. 3.11.54. Female, aged 22. 16th coma, insulin dose 176 units. This patient failed to respond to i.g. glucose and to i.v. glucose given later. She had been in coma about 6 hours when I saw her and was very collapsed. The only significant abnormality in her blood chemistry was in the serum bicarbonate, 15 mN. She failed to respond to two separate doses of 50 mg. of ACTH and died in the 4th week of coma from apparent exhaustion.

Along with the cases in recovery groups 4 and 5, where coma was prolonged into days and weeks, the four cases that died raise the question of whether it would be useful to continue using hormones after the first day of coma. In case 48, cortisone given late did not help. It might have helped in the other three. This would be easily practicable now that long-acting ACTH is available. Death may arise from other causes than adrenal exhaustion, as is shown by case 48, and each case would have to be treated according to its needs.

(8) Value of B-vitamins. The B-vitamins are undoubtedly of value, if given in adequate amounts. The commonest abnormality in the blood found in the early stages of prolonged insulin coma is an increase in pyruvate. It was found in 34 (80 per cent.) of 42 cases in which it was estimated, and in most of these the blood cocarboxylase was artificially high as a result of vitamin injections. In some cases the pyruvate increased as the coma was extended and more and

more glucose was given. Low blood cocarboxylase was found in 2 cases. As has been pointed out previously, quoting Kay, Murfitt and Glatt (1959), the raising of the blood cocarboxylase by giving thiamine does not necessarily immediately restore to normal the enzyme activity which depends on the presence of adequate co-enzyme formed from thiamine. This is particularly true if activity or the metabolism of extra glucose occurs.

In B-vitamin deficiencies, usually more than one factor is deficient. Although tests for deficiencies of factors other than thiamine were not carried out in this work (except for co-enzyme I in a few cases), it was best to act on the assumption that there was depletion of the remaining B-vitamin factors. (It should be noted that the method of estimating blood cocarboxylase (Kay and Murfitt, 1956) was worked out for use in this study of prolonged insulin coma.) The three B-vitamins required for co-enzyme synthesis, thiamine, nicotinamide and riboflavin must be included. Pyridoxin was used, since claims are made that it has value in toxic comas. Pantothenic acid was included because there is some evidence that it is necessary for proper function of the adrenal cortex and the production of its hormones (Bean *et al.* 1955, Eisenstein, 1955). Vitamin B₁₂, even in milligram doses, did not appear to have any effect on the course of recovery.

(9) Accessory treatment. The other therapeutic measures taken were chiefly for the purpose of restoring the blood glucose and electrolytes to normal levels and to keep them there. Both hormones, and repeated i.v. infusion of salines, tend to raise the plasma sodium and chloride, excessive elevation of which may cause oedema of the lungs. Intravenous infusion of glucose tends to lower the concentration of the plasma potassium; so do the hormones. Low plasma potassium concentrations are a danger to proper cardiac action. Often in prolonged coma the plasma bicarbonate falls, sometimes to dangerous levels. Acidosis embarrasses respiration and probably facilitates cerebral damage. When the plasma bicarbonate is moderately low or very low, i.v. infusion of 50 per cent. sodium lactate is invaluable. Dehydration, or increase of blood concentration may occur and embarrass the circulation. All these variations in the "milieu interne" can only be accurately detected by appropriate laboratory investigations, upon which rational treatment can be based.

In addition to the foregoing, the usual routine measures for treating shock and collapse were applied as appeared clinically necessary.

V. BIOCHEMICAL FINDINGS

Brief summary of abnormalities found

Biochemical investigations were carried out in 56 of the 62 cases to help in assessing the state of patients' "milieu interne" and to guide treatment. Examples of results are given in the Appendix.

In addition to their use in guiding treatment, the systematic chemical investigations have cleared up some uncertainties. Alkalosis, often said to occur, was never found; on the contrary, a low plasma bicarbonate was so frequent as to make it safe to act on the assumption that it was present, when treatment had to be started without laboratory results. Deficiency of B-vitamins was very frequent, as judged from blood pyruvate values, even though the blood cocarboxylase was artificially high as the result of administering B-vitamins.

It was not possible to apply the full battery of tests in every case, but in most cases, especially in those with delayed recovery, repeat tests were done. I am not aware of any published similar systematic work with which comparisons

can be made. It is proposed now only to summarize the most important findings in the early investigations in each case, the meanings of which will be self-evident.

Serum sodium:	low in 6 cases; high in 1.
Serum potassium:	low in 6 cases; high in 3.
Serum chloride:	low in 0 cases; high in 14.
Serum bicarbonate:	low in 25 cases; high in 0.
Serum uric acid	low in 0 cases; high in 22.
Blood pyruvate:	low in 0 cases; high in 34.
Blood cocarboxylase:	low in 2 cases; high artificially in many.
Urine ketosteroids:	low in 6 cases; high in 0.

It is evident that the main findings are the loss of plasma bicarbonate, which is related to changes in oxidation processes (oxyachrestia) and, with low serum sodium, to adrenocortical failure, and the increase in blood pyruvate, which is evidence of disturbed enzyme reactions dependent on thiamine. It is essential to deal with both these disturbances to aid recovery.

Knowledge of the blood glucose level is, as has been pointed out, essential for treatment. Results are not discussed here because most patients had had i.v. glucose when first seen.

The raised serum uric acid is a new finding. The highest value found was 20.8 mg./100 ml. Raised values decline in course of time after recovery. I have found raised values, sometimes as high as this, in some normal insulin comas, the initial level being normal but followed by a steady increase throughout the coma with a fall after recovery following successful interruption of coma. This does not occur in all comas. The increase in blood uric acid may be related to nuclear damage caused by the coma process and to low activity of the adrenal cortex.

It was possible to investigate ketosteroid output in only 7 cases. All values except one were low. The one exception was in the normal range, but represented the 24-hours' excretion following the injection of ACTH to rouse the patient from prolonged coma (Case 13). The results support the argument for adrenocortical fatigue. In some cases, as the patient recovered from the effects of the prolonged coma, the 17-ketosteroid output rose.

Serum cholinesterase values were mostly normal but two cases had high normal values of pseudo-cholinesterase. This has also been found in normal insulin comas (personal observations).

There was occasionally an increase in serum globulins, especially in the longer cases. This may be related to the toxic state.

Not many estimations of blood glutathione were done. In two cases results were normal (29.8, 31.2 and 33.9 mg./100 ml.). On the other hand, one patient had values of 77-90 mg./100 ml. and another 65 mg./100 ml. These values did not seem to be related to blood glucose level or be affected by giving hormone. Blood glutathione is concerned in some oxidation reactions and may be related to the secretion of insulin. Further investigations are needed on this aspect of coma.

Although not biochemistry, the haematological findings may be referred to here. The red cell count, haemoglobin estimation and packed-cell volume are useful in conjunction with the total serum protein value to assess the state of hydration of the body. One difficulty in interpretation is the absence of values in the normal state of the patients. Almost invariably the white blood cell count

increases in comas lasting more than a few hours. The increase is chiefly in the polymorphoneutrophils. This phenomenon usually subsides as the patient recovers and may be due to tissue damage, or as some say, to the toxic effects of insulin. It is accompanied by a pyrexia, sometimes high, which is due in part to tissue damage, especially cerebral, and in part to the increased combustion of glucose. This early pyrexia subsides without special treatment. Leucocytosis and pyrexia occurring later, say after 3 or 4 days in the longer comas, usually indicates an infection, most likely pneumonia.

VI. SUMMARY OF TREATMENT

Summary of treatment

It is possible now to summarize the method of treatment in cases of prolonged insulin coma which have failed to respond to glucose given intravenously.

- (1) Assess the case clinically.
- (2) Take blood for laboratory investigations: estimations of blood glucose, plasma electrolytes and proteins, blood count, haemoglobin and packed-cell volume. Repeat these as required, but blood glucose estimations should be done approximately hourly.
- (3) Give adequate mixed B-vitamins, if not already given.
- (4) If the blood glucose is low, give $33\frac{1}{3}$ per cent. glucose in saline i.v.
- (5) Give 50 mg. of cortisone or ACTH i.m. Repeat in about 1 hour if necessary, making sure that the blood glucose is over 100 mg./100 ml. In cases that need a second dose of hormone, an additional dose of 100–120 mg. ACTH-gel is useful for an effect of long duration.
- (6) If recovery does not occur within about half an hour, institute intragastric feeding: water 10 oz. (300 ml.), glucose 50 g., potassium chloride 2 g., sodium bicarbonate 4 g., repeating every two hours, first withdrawing and measuring any residues of the feed last given. Adjust content of meals in accordance with changes in blood chemistry. Use i.v. sodium lactate to correct low plasma bicarbonate. Continue until recovery or for 24 hours then start nutrient feeds.
- (7) Should recovery not take place by the second day, institute a regime of regular i.g. feeds based on milk, which should be citrated or otherwise treated to prevent clotting till the risk of vomiting has passed. The feeds should provide adequate proteins, glucose, salts, vitamins, calories and water.
- (8) Use penicillin in adequate doses from the first day to prevent pneumonia.
- (9) At all times be ready to treat cardio-respiratory collapse.
- (10) Watch for distension of the bladder and catheterize if necessary.
- (11) Adjust intake, intravenous and intragastric, in accordance with blood chemistry.
- (12) Avoid high glycaemia, dehydration and low plasma bicarbonate especially.

VII. CONCLUSIONS

Conclusions

(1) Two important factors related to the onset of prolonged insulin coma are fatigue of the anterior-pituitary-adrenocortical system and disturbance of the oxidation mechanisms dependent on co-enzymes derived from B-vitamins.

(2) The administration of cortisone or ACTH to patients in prolonged insulin coma after raising the blood glucose to at least normoglycaemia assists their recovery, quickly rousing a large proportion to full recovery and stabilizing the blood glucose in others, thus preventing relapses into hypoglycaemia. Both hormones are valuable therapeutic agents in this connection and worth routine use when necessary.

(3) B-vitamins, preferably thiamine, nicotinamide, riboflavine, pyridoxine and pantothenic acid, are useful for routine use.

(4) Recovery is not affected by the dose of insulin used to induce coma, nor by the interval between onset of coma and giving of hormone up to a period of about 9 hours. On the other hand, the less the period of hypoglycaemia is prolonged, the better is the chance of quick recovery. Primary interruption by intravenous glucose is better than by intragastric. The patients who had had most comas tended to recover quickest.

(5) Prolonged comas tend to occur most frequently in the early part of the treatment course, at periods when low ketosteroid excretion occurs, and in the middle and second half of the week.

(6) Some patients having a second or third course of comas are likely subjects for a prolonged coma.

(7) Death, when it occurs, may be due to collapse, exhaustion or pneumonia.

(8) Treatment, apart from using hormones and vitamins, should be controlled by adequate laboratory investigations.

(9) Management of the blood glucose and electrolytes is essential where recovery is delayed beyond 2-3 hours after giving hormone. Sodium bicarbonate by gavage or sodium lactate i.v. corrects low plasma bicarbonate.

(10) Gastric stasis, almost invariably present in prolonged coma, does not respond to the usual drugs used to relieve spasm or produce movement of the alimentary tract.

(11) Methedrine does not rouse patients but causes excessive motor activity which may exhaust the patient. It should not be used.

The conclusions that both cortisone and ACTH are useful and an advance on previous empirical methods of treatment is inescapable, especially when one has seen the dramatic recovery made by some patients within 15 to 20 minutes after injecting the hormone. The 55 cases treated with hormone had failed to recover after the usual methods of treatment. Twelve of these recovered within an hour after being given hormone and in many cases their recovery was little different from the normal manner of recovery they had shown in their previous uneventful comas. Ten cases recovered within a few hours after receiving hormone, having first shown early progress by the lightening of their coma and by developing a stable blood glucose, and 18 cases recovered by the next day. The relief of anxiety over these cases is inestimable.

Little attempt was made to choose a hormone for any case. Cortisone appeared to act better than ACTH when the extra period of hypoglycaemia was short, especially after i.v. primary interruption. In other cases it was at least as good as ACTH. It was therefore acceptable as first choice to use in any case, especially when it was more generally available than ACTH. Now that both hormones are available, either can be used with almost equal hope of success. ACTH-gel (long-acting) is now available and is useful to give slow, continuous

stimulation of the adrenal cortex when the first dose of hormone fails to rouse the patient in 3-4 hours.

During the course of this work, it soon became apparent that although both hormones stabilized the blood glucose level, and sometimes even raised it, they did not rouse patients from coma unless the blood glucose was near, in or above the normal range. This was confirmed by investigations on a series of patients undergoing insulin coma treatment (Kay, 1958). ACTH or cortisone was given at different stages of coma in different patients. Both hormones sometimes roused patients from light coma but not from deep coma until glucose was given i.v. Then a normal recovery occurred even though the deep coma had been prolonged at least an hour.

The "prompt" recoveries induced by ACTH and cortisone suggest that both hormones have some action besides that of counteracting insulin and stabilizing the blood glucose level. They roused the patient so quickly and so completely that they appeared to have a stimulating effect on the cerebral cortex. Methedrine, a known cerebral cortical stimulant, did not rouse patients; it produced excessive and unwanted motor activity.

One hospital still using insulin coma treatment, that provided many of the cases included in this report, has accepted hormone treatment as a routine for patients who do not respond normally to their primary interruption and has found it very satisfactory.

VIII. SUMMARY

Summary

(1) The types, treatment, aetiology and pathology of prolonged insulin comas are discussed.

(2) The significance of fatigue of the anterior-pituitary-adrenocortical system and of the disturbance of the oxidative enzyme systems depending on B-vitamin co-enzymes in relation to prolonged insulin comas is indicated.

(3) An account is given of experience of 62 cases of prolonged insulin coma, 55 of which were treated with cortisone and/or ACTH.

(4) Twelve of these cases recovered in less than one hour after receiving hormone, and ten others within a few hours after. Four deaths occurred.

(5) Initiation of recovery by both hormones appears to be an improvement on previous methods of treatment.

(6) The rationale of the use of hormones in treating prolonged coma and some factors affecting results are discussed.

(7) The method of treatment is stated together with an account of the laboratory investigations that should accompany it.

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IX. APPENDIX

Case No. 1. Male, aged 28. Insulin 230 units. 4.5.51.

Blood Glucose:	165 mg. %	Serum Proteins:	Total Albumin	6.0 g. %
Serum Sodium:	156 mN		Globulin	5.1 g. %
			A/G	0.9 g. %
Serum Chloride:	106 mN	Blood Lactate:		6.0/1
Serum Bicarbonate:	21 mN	Blood Pyruvate:		>60 mg. %
Serum Phosphates:	0.8 mN	Blood Urea:		6 mg. %
Blood P.C.V.:	42 %			25 mg. %

Case No. 3. Female, aged 23. 2nd coma: insulin 280 units.

Serum Chlorides:	mN	2.4.52	3.4.52	4.4.52	7.4.52	16.4.52	29.4.52
Serum Bicarbonate:	mN	1.15 p.m.	3.40 p.m.	10.20 a.m.	10.05 a.m.	12.15 p.m.	
Blood Glucose:	mg. %	103.5	104	105	102	102	96
Serum Potassium:	mN	28	25	28	29	27	27
Serum Sodium:	mN	111	77	206	82	—	—
Serum Phosphates:	mN	4.6	4.1	3.8	3.5	4.6	4.5
Serum Urea (Blood):	mN	152	150	155	154	150	143
Serum Protein:	mg. %	0.6	0.5	0.9	0.7	1.35	1.35
Total Albumen	g. %	17	14	29	31	27	24
Globulin	g. %	—	5.9	6.0	—	6.3	7.4
A/G ratio	g. %	—	4.1	4.0	—	4.2	4.5
Blood Co-enzyme I:	μg. %	—	1.8	2.0	—	2.1	2.9
Blood Pyruvate:	mg. %	—	2.3	2.0	—	2.0	1.5
Blood Carboxylase:	μg. %	37.0	32.5	36.9	32.0	37.6	33.6
Serum Cholinesterase:	units	2.18	3.26	2.12	0.61	1.42	1.1
Serum Cholesterol:	mg. %	21.5	18.3	23.2	22.5	11.6	15.9
Free	mg. %	55.6	54.4	49.7	44.0	—	53.0
Ester	mg. %	—	—	—	—	105	265
F/E ratio	mg. %	—	—	—	—	40	85
Urine 17-Ketosteroids:	mg./24 hrs.	7.4.52	9.4.52	25.4.52	6.5.52	8.7.52	Recovered
Urine volume:	ml./24 hrs.	4.4	3.2	6.8	5.3	13.7	13.7
		900	900	790	2230	980	980

Slight albuminuria with few r.b.c's

True cholinesterase normal throughout.

Case No. 4. Male, aged 28. 33rd coma: insulin 380 units.

		1.5.52 Coma day				2.5.52 Post-coma
		4.5 p.m.	5.0 p.m.	6.5 p.m.	8.45 p.m.	11.40 p.m.
Blood Glucose:	mg. %	65	90	115	250	147
Serum Sodium:	mN	150	158	150	150	144
Serum Potassium:	mN	4.4	3.8	4.4	4.3	4.1
Serum Chloride:	mN	108	112	108	108	102
Serum Bicarbonate:	mN	29.0	27.0	29.0	28.5	29.5
Serum Phosphates:	mN	0.6	0.6	1.0	1.4	1.45
Serum Protein: Total	g. %	7.2	7.3	7.1	6.8	6.6
Albumen	g. %	4.4	4.5	4.5	4.3	4.1
Globulin	g. %	2.8	2.8	2.6	2.5	2.5
A/G ratio	..	1.6	1.6	1.7	1.7	1.6
Blood Urea:	mg. %	34	31	27	31	31
Blood Pyruvate:	mg. %	0.83	0.96	0.92	4.42	1.36
Serum Cholesterol: Total	mg. %	190	185	185	155	160
Free	mg. %	70	60	60	50	55
Ester	mg. %	120	125	125	105	105
F/E	ratio	1.7	2.1	2.1	2.1	1.9
Serum Uric Acid:	mg. %	13.6	12.4	12.0	9.2	7.0
Urine 17-Ketosteroids:	mg./24 hrs.	..	3.5.52	..	..	8.5.52
Urine volume:	ml./24 hrs.	..	8.4	..	..	12.7
		..	1700	..	..	3850

Recovered

4.35 p.m. 25 mg. cortisone i.m.

Case No. 12. Female, aged 34. 4th coma; insulin 40 units.

Serum Sodium:	..	..	..	16.12.52 12.45 p.m.	16.12.52 2.0 p.m.	16.12.52 3.30 p.m.	17.12.52 2.0 p.m.
Serum Potassium:	mN ..	..	..	149.1	152.6	148.2	146.5
Serum Chlorides:	mN ..	..	..	4.3	4.3	4.2	4.5
Serum Bicarbonates:	mN ..	..	..	103	105	104	106.5
Serum Phosphates:	mN ..	..	..	27.0	27.5	27.0	28.5
Serum Urea (Blood):	mN ..	..	..	1.3	2.1	1.3	1.6
Serum Uric Acid:	mg. %	..	..	24	22	22	21
Serum Proteins: Total	g. %	..	..	4.8	4.9	4.8	4.0
Albumen	g. %	..	..	7.1	7.0	6.9	6.9
Globulin	g. %	..	..	4.3	4.4	4.4	4.3
A/G ratio	g. %	..	..	2.8	2.6	2.5	2.6
Blood Pyruvate:	mg. %	..	..	1.5	1.7	1.8	1.7
Blood Cocarboxylase:	μg./100 ml.	..	..	1.8	1.2	—	1.0
Blood Thiamine:	μg./100 ml.	..	..	9.4	10.5	—	8.9
Urine 17-Ketosteroids:	mg./24 hrs.	..	..	0.4	0.9	—	0.9
Urine volume:	ml./24 hrs.	..	..	—	—	—	2.4
Blood Glucose:	mg. %	..	..	70	83	115	830
						2.05 p.m. Cortisone 25 mg. i.m.	—
						12.45 p.m. Cortisone 25 mg. i.m.	—
						Recovered	—

Case No. 13. Female, aged 28. 3rd coma: insulin 190 units.

Serum Sodium:	mN	..	..	..	..	17.12.52 12.35 p.m.	12.40 p.m. ACTH 25 mg. i.m.	17.12.52 1.43 p.m.	Recovered	18.12.52 12.15 p.m.
Serum Potassium:	mN	..	..	..	..	137.8		146.4		146.9
Serum Chloride:	mN	..	..	..	..	4.8		3.8		4.8
Serum Bicarbonate:	mN	..	..	..	..	103.2		108.7		106.0
Serum Phosphates:	mN	..	..	..	..	20.5		20.5		27.0
Blood Urea:	mN	..	..	..	..	1.6		1.6		1.3
Serum Uric Acid:	mg. %	..	..	..	..	22		21		21
Serum Proteins:	g. %	..	..	..	..	3.6		4.2		4.0
Albumen	g. %	..	..	..	..	6.7		7.1		6.0
Globulin	g. %	..	..	..	..	4.4		4.5		3.6
A/G ratio	g. %	..	..	..	..	2.3		2.6		2.4
Blood Pyruvate:	mg. %	..	..	..	..	1.9/1		1.7/1		1.5/1
Blood Cocarboxylase:	μg./100 ml.	..	..	..	..	1.7		3.0		1.3
Blood Thiamine:	μg./100 ml.	..	..	..	..	7.8		8.2		6.5
Blood Glucose	mg. %	..	..	..	..	0.7		0.4		0.6
Blood P.C.V.:	%	..	..	..	..	605		350		—
Urine 17-Ketosteroids:	mg./24 hrs.	..	..	..	..	—		—		34
Urine volume:	ml./24 hrs.	..	..	..	..	19,12.52		8.5		—
		..	..	..	..	2970		—		—

Case No. 16. Female, aged 28. 2nd coma: insulin 250 units.

Serum Sodium:	mN	..	..	..	..	25.2.53	5.55 p.m.	5.55 p.m. 50 mg. Cortisone i.m.	25.2.53	26.2.53	Recovered
Serum Potassium:	mN	..	..	..	..	5.50 p.m.	147.8		153	153	
Serum Chloride:	mN	..	..	..	..	—	—		2.6	3.0	
Serum Bicarbonate:	mN	..	..	..	..	105.2	—		104.3	105.2	
Serum Phosphates:	mN	..	..	..	..	14.5	—		23.0	28.0	
Serum Uric Acid:	mg. %	..	..	..	..	1.0	—		2.0	1.6	
Blood Urea:	mg. %	..	..	..	..	6.4	—		5.8	3.3	
Serum Proteins:	g. %	..	..	..	..	—	—		17	21	
Albumen	g. %	..	..	..	..	—	—		—	6.4	
Globulin	g. %	..	..	..	..	—	—		—	3.8	
A/G ratio	..	..	..	..	..	—	—		—	2.6	
Blood Glutathione:	mg. %	..	..	..	..	—	—		—	1.5/1	
Blood P.C.V.:	%	..	..	..	..	—	—		—	65	
Blood Glucose:	mg. %	..	..	..	..	—	—		—	38	
		..	..	..	..	5.30 p.m.	394		6.15 p.m.	7.50 p.m.	
		..	..	..	..				348	212	

A CLINICAL AND BIOCHEMICAL STUDY OF MONOAMINE OXIDASE INHIBITION IN DEPRESSED PATIENTS

I. A CLINICAL TRIAL OF NIALAMIDE

By

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THE discovery that iproniazid benefits certain subjects with depression, linked with the demonstration that it inhibits the enzyme monoamine oxidase (MAO), led to the hypothesis that inhibition of MAO was the essential mechanism by which iproniazid caused relief of symptoms (Pletscher, 1959). Iproniazid, unfortunately, can produce serious toxic effects, particularly on the liver (Pare and Sandler, 1959), and this has limited its clinical application. For this reason a search has been made for MAO inhibitors with an effective anti-depressant action yet without the serious toxic effects of iproniazid. Among the newer compounds for which such claims have been made is N-isonicotinoyl (-N-N-benzylcarboxamidoethyl) hydrazine or Nialamide.

This paper describes a clinical trial of Nialamide in depressed patients in an effort to assess its clinical efficacy and the incidence of side-effects.

METHODS

1. Assessment of Anti-depressant Effect

In addition to the normal clinical routine of history, examination and day to day surveillance, the registrars in charge of each case were asked to rate the patient's progress at weekly intervals. Five main items (depressive mood, retardation, socialization, sleep and appetite) were assessed week by week on a simple four-point scale. Information was also asked about other symptoms such as ideas of reference, hypochondriasis, etc.

As many of the patients were severely depressed, it was not considered justifiable to start treatment with placebo. For this reason a modified double-blind procedure was used. All patients were initially given the active drug in a minimum dosage of 25 mg. three times daily for 2 weeks followed by 50 mg. three times daily for a further two weeks. At some time thereafter, unknown to the patient, the doctor and the nurses in charge of the case, placebo was substituted. These tablets were identical in appearance and taste to the active preparation. As it turned out, the active drug was remarkably free from side-effects in the dosage used and consequently the substitution of placebo could not readily be detected by either patient or the medical attendants. If a worsening of the patient's condition occurred after being put on placebo, the active drug was again exhibited.

From this it will be apparent that a patient may improve on the drug, relapse on placebo and again improve when the active drug is re-introduced.

These patients have been called true responders. Again, a patient may improve on the drug but maintain this improvement whilst on placebo for periods of time which are longer than can be explained by a hangover effect. These cases are called coincidental responders. Finally, patients may either show no response to the drug or respond for a time, relapse on placebo and thereafter show no further improvement when given the active drug again. These patients are designated as non-responders.

2. Assessment of Toxic Effects

(a) *Clinical.* The registrars in charge were asked to report any side-effects of the drug and the rating form contained a list of possible sequelae such as oedema, difficulty in micturition, etc., derived from previous experience with iproniazid (Pare and Sandler, 1959b). In addition patients were weighed weekly and the blood pressure in the lying and standing positions was recorded periodically to note the supervention of postural hypotension.

(b) *Biochemical.* Routine blood counts were supplemented by serial estimations of both glutamic-oxaloacetic and glutamic-pyruvic transaminase usually at fortnightly intervals (method of Reitman and Frankel, 1957).

CASE SELECTION AND ANALYSIS OF MATERIAL

The only criterion for admission to the study was that the patient should be unequivocally depressed in the absence of any other complicating mental illness such as schizophrenia or organic psychosis. It was deliberately intended that as wide a clinical range of depressive conditions as possible be studied in this preliminary survey in order to provide possible pointers for future work. The patients were taken from the day to day in-patient and out-patient practice of the hospital, the consultants in charge deciding whether or not a patient should be admitted to the trial. Thirty-four patients were initially admitted, but six did not complete the course for the following reasons; non co-operation (2), transfer to other treatment by the consultant (3), self-discharge (1). The present report concerns the data obtained from the remaining 28 patients. The details of these patients are summarized in Table I. Many of the patients had failed E.C.T. or other drug therapies in the course of the present illness and were difficult therapeutic problems.

TABLE I
28 Cases of Depression Treated With Nialamide

					True Improvers		Coincidental Improvers		Non-Responders	
No. of patients	..	..	..	..	4		3		21	
Age: mean	..	..	..	..	54.25		47.3		46.5	
range	..	..	..	..	38-65		40-55		22-65	
Sex	..	..	..	..	3 F	1 M.	2 F.	1 M.	11 F.	10 M.
In-patients	..	..	..	..	2		0		10	
FH of depression	..	..	..	..	0		1		8	
Previous depressive illnesses	..	..	..	..	1		1		8	
First attack after 40 years of age	..	..	..	..	3		1		12	
Length of present illness (months)	..	..	..	..	24		51		61	
Aetiological factors of importance:										
Physical	..	..	..	..	2		0		4	
Constitutional	..	..	..	..	3		3		9	
Environmental	..	..	..	..	1		0		6	

Results

Of the 28 patients, 7 improved, but only 4 of these fulfilled the criteria described above for cases designated as responding to treatment with Nialamide. These patients could all be classified as "endogenous" depression but showed no clinical characteristics to distinguish them from other such cases in whom environmental precipitating factors were inconspicuous. None of the 4 cases improved during the first 2 weeks of treatment, improvement only becoming manifest when the dosage had been increased to 150 mg. daily. The degree of improvement in 3 of these 4 "responders" was marked, and comparable to that which one expects to find after E.C.T. However it should be emphasized that, in contrast to E.C.T., there was no evidence that Nialamide cured the depression, but rather that it afforded symptomatic relief as long as the drug was continued or until a natural remission occurred.

Toxic Effects

(a) *Clinical observations.* No symptoms referable to the drug were reported in any of the 28 cases. Serial measurements of the blood pressure showed no evidence of postural hypotension in any patient. Weekly weighings were carried out to check the development of latent oedema. Nineteen of the 21 non-responders remained within 3 lb. of their initial weight. A further patient gained 4 lb. and another lost 7 lb. Of the patients who showed a "true response", 2 had increases of body weight of 10 lb. and 31 lb. The weight gains were acquired gradually over a period of 6 months and were thought to be due

TABLE II

Summarizing the Values for Glutamic-oxaloacetic Transaminase (G-OT) and Glutamic-pyruvic Transaminase (G-PT) before and during Treatment with "Nialamide"

Case No.	Initial	Maximum	Final	Initial	Maximum	Final
1	10	25	15	5	10	10
3	15	32	20	10	15	15
4	10	32	18	20	20	10
5	15	48	25	10	20	20
6	15	15	15	10	10	10
7	11	20	15	12	13	13
8	18	18	7	13	13	8
9	7	20	13	15	17	10
10	10	35	10	5	15	15
11	25	25	10	25	25	17
12	5	15	5	5	15	5
13	18	36	36	10	22	22
14	8	22	22	5	15	15
15	15	25	25	15	25	25
16	6	21	10	5	20	17
17	70	70	17	25	25	15
18	12	15	15	10	15	15
19	60	70	30	85	85	40
20	40	40	20	30	30	20
21	20	225	225	20	235	235
22	10	20	15	5	20	20
23	30	35	10	20	20	10
24	11	26	26	8	35	24
25	39	39	6	16	20	5
26	20	30	20	10	25	25
27	20	20	20	10	30	30
28	10	10	10	5	10	10

to the improvement in the mental state. The remaining 5 showed no weight change.

(b) *Laboratory findings.* Routine blood counts revealed no evidence of toxic effects.

All but one of the 28 patients had serial estimations of both glutamic-oxaloacetic transaminase (G-OT) and glutamic-pyruvic transaminase (G-PT). The results are given in Table II for each enzyme. The first column gives the level at the start of treatment, the next the maximum reading at any time during the investigation and the third the final level at the end of the trial. In the case of the failures the period of time elapsing between the initial and final readings varied from 6 to 8 weeks whereas the patients who responded, naturally received the drug for a longer time. Of particular interest therefore, are patients 17 and 18, both of whom received the drug for 6 months in average dosage of 200 mg. daily and in neither of whom was there a significant increase in transaminase levels.

Only one of the 27 patients showed a definite departure from normality, namely Case 21. This lady of 42 years is worthy of further comment. The detailed transaminase readings are given below:

Date	G-OT	G-PT
8 April	17	24
20 April	15	12
29 April	32	38
6 May	20	20
13 June	32	38
29 June	65	80
27 July	84	125
10 August	122	145
7 September	225	235

Full liver function tests done on 27 July were normal and at no time has the patient shown any clinical evidence of liver damage. She had been treated from 6 April to 6 May with iproniazid 150 mg. daily. On 11 May treatment with Nialamide was started and this was continued until 24 June. During this time her depression improved and placebo was substituted. However, after 7 days, she relapsed and 2 days later the active drug was re-introduced. This was continued until 25 July when it stopped as the patient did not show her previous symptomatic improvement. The dosage of Nialamide over the 55 days was increased gradually and over the whole period totalled exactly 7,000 mg. gross—an average of just over 100 mg. a day.

Taking the remaining 26 cases together, the most common finding was a slight rise in both G-OT and G-PT levels. This could occur as early as the fourth day after starting therapy but in some was delayed for 30 days. However, this rise rarely exceeded the upper limits of normal and almost as common was a slight fall in levels. In order to clarify these findings further, comparisons were made between the initial and final readings for each enzyme. This showed that there was no significant difference for either G-OT ($P > 0.4$) or G-PT ($P > 0.8$).

DISCUSSION

It is inevitable and indeed salutary that new monoamine oxidase inhibitors should be compared against iproniazid, about which so much is known (Symposium, 1958).

Although only 4 of the 28 depressed patients in this investigation were thought to have improved as a result of the drug, it should be noted that in none of the 4 were environmental precipitating factors conspicuous. In fact of the 17 patients in this series who could be labelled "endogenous", 25 per cent. responded to Nialamide. This is a similar proportion to that obtained in a previous investigation with iproniazid, where the patients studied were limited to those considered suitable for E.C.T. (Pare and Sandler, 1959).

In the dosage used there was no convincing evidence that Nialamide gives rise to toxic effects. One patient developed a marked rise in serum transaminase but this remained high and even increased as long as 6 weeks after the drug was stopped. A similar rise has been observed in the absence of active medication by other workers (Rees and Davies, personal communication). The fact that none of the other patients showed a significant rise in serum transaminase is in marked contrast to the findings with iproniazid (Pare and Sandler, 1959a) and suggests that the abnormal transaminase values in this one patient were coincidentally, rather than causally, related to the Nialamide therapy.

SUMMARY

A controlled double-blind trial of Nialamide has been carried out in 28 depressed subjects. Seven patients showed improvement and in 4 of these the improvement was attributed to the drug. In these 4 patients environmental precipitating factors were inconspicuous.

In the dosage used, no clinical toxic effects were observed and only one patient showed any significant rise in transaminase levels. In this respect the drug appears to be appreciably safer than iproniazid in its short term toxic effects.

ACKNOWLEDGMENTS

We are indebted to those physicians who allowed us to study their patients and to Dr. J. K. Morrison of Messrs. Pfizer Ltd. for supplies of Nialamide.

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A CLINICAL AND BIOCHEMICAL STUDY OF MONOAMINE OXIDASE INHIBITION IN DEPRESSED PATIENTS

II. 5-HYDROXYTRYPTAMINE TOLERANCE BEFORE AND AFTER NIALAMIDE

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IN order to test whether a drug is an inhibitor of monoamine oxidase in the human subject, three main measures are available:

1. We can measure an increased excretion of the normal substrates of the enzyme, e.g. tryptamine (Sjoerdsma, *et al.*, 1959b).

2. We can measure a decreased excretion of the metabolites resulting from the enzyme's action, e.g. 5-hydroxyindoleacetic acid (5-HIAA).

3. We can administer a loading dose of an enzyme substrate and observe how the subject deals with it before and after the drug, e.g. 5-hydroxytryptamine (Sjoerdsma *et al.*, 1958), and epinephrine (N-methyl-C¹⁴) (Resnick *et al.*, 1958).

The disadvantage of the second method is that the metabolites may be present in such low concentration that accurate measurement with our present methods is not possible on hourly or two-hourly specimens of urine. Such measures were made on our patients and the hourly excretion of 5-HIAA in urine varied between 0.69 and 0.00 mg. After receiving the drug these values fell, as was to be anticipated, but in many instances the amount was too small to be recorded in two-hourly specimens. As the role of 5-hydroxytryptamine (5-HT) in the aetiology of depression is still uncertain, we chose the third method for estimating monoamine oxidase (MAO) activity, using 5-HT as the substrate and assaying its major metabolite, 5-HIAA, in the urine.

METHOD

The test was performed on 18 of the 28 depressed patients described elsewhere (Dewhurst and Pare, 1961). In addition, two normal volunteers had tests before and after the drug. The subjects were given N-isonicotinoyl (N-N-benzylcarboxamidoethyl)hydrazine, or Nialamide, as an anti-depressant drug for periods of at least 4 weeks and in a minimum dosage of 75 mg. daily for 2 weeks followed by 150 mg. daily for a further 2 weeks; the drug was given three times daily. A 5-HT tolerance test was carried out before and during treatment with the drug.

For 24 hours before the tests the patient was put on a diet from which foods known to contain large amounts of serotonin were excluded (Udenfriend *et al.*, 1959). On the morning of the test the bladder was emptied and an hour

later the bladder was emptied again. This specimen was saved to give a measure of the basal excretion of 5-HIAA. Also at this time a capsule of 5-HT creatinine sulphate containing 10 mg. of 5-HT was given by mouth. Urine was collected 2, 4, 6, and 8 hours later and 5-HIAA estimated (blind) by the method of Udenfriend *et al.* (1955).

RESULTS

Basal excretion of 5-HIAA. As stated above, the hourly excretion ranged from 0.69 to 0.00. After Nialamide this range fell and in many instances 5-HIAA could not be detected. No reliable distinction between patients could be made on this basis.

Response to 5-HT load. The total 8-hour excretion of 5-HIAA before and after Nialamide for the 20 subjects studied is given in Table I. Taking all 20

TABLE I

Showing the 8-Hour Excretion of Urinary 5-Hydroxyindoleacetic Acid (mg.) After an Oral Load of 10 mg. 5-Hydroxytryptamine, Before and During Treatment with Nialamide

	A Before Nialamide	B After 75 mg. Nialamide for 14 Days	Ratio A/B	
Normals				
1 ..	4.5	5.1	0.9	
2 ..	4.9	4.6	1.1	
Case No.				
1 ..	4.6	4.2	1.1	
2 ..	3.8	4.6	0.8	
3 ..	8.4	0.8	10.5	
4 ..	9.2	2.8	3.0	
5 ..	6.3	0.3	21.0	
6 ..	4.0	1.9	2.1	
7 ..	5.7	2.2	3.9	
8 ..	1.7	2.1	0.8	
9 ..	4.4	3.4	1.3	
10 ..	5.5	3.2	1.7	
11 ..	3.2	3.9	0.8	
12 ..	6.4	5.0	1.2	
13 ..	6.7	1.0	6.7	
14 ..	1.7	0.2	8.5	
15 ..	5.2	2.4	2.2	
16 ..	1.3	1.1 (After 14 days on 100 mg. Nialamide a day)		
17 ..	1.7	1.7 (After 50 mg./day for 20 days and 100 mg./day for 6 days)		
18 ..	3.6	3.4 (After 100 mg./day for 13 days, 150 mg./day for 14 days and 200 mg./day for 8 days)		
				8-Hour 5-HIAA After Nialamide 150 mg. for Further 14 Days
				4.8
				2.6
				4.4
				1.0
				1.8
				3.0

subjects together the reduction in 5-HIAA excretion after the drug is statistically significant ($p < 0.01$). However the excretion of urinary 5-HIAA following oral ingestion of 5-HT depends not only on its metabolism by MAO but also on the rate of absorption from the gastrointestinal tract. Usually the greater

proportion of the 8-hour 5-HIAA was excreted within the first 4 hours and only a small amount in the 6-8 hour period and in these cases, we felt, the effect of absorption from the gastrointestinal tract could be ignored. In some cases after Nialamide this was not true. Where over 30 per cent. of the 8-hour production of 5-HIAA was excreted in the final 2 hours, the possibility of delayed absorption from the alimentary tract could not be ignored and the 5-HIAA excretion in these cases (4, 12, 14) cannot be considered a reliable index of MAO activity (Table II). Excluding these 3 patients, and the 2 normal

TABLE II

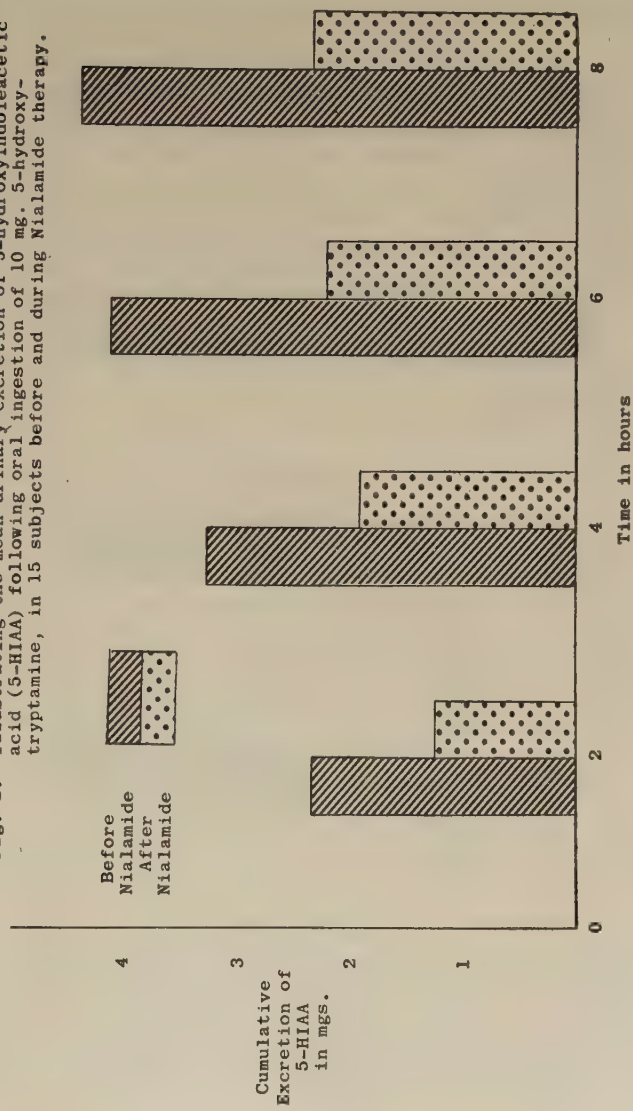
Excretion of Urinary 5-Hydroxyindoleacetic Acid After an Oral Load of 10 mg. 5-Hydroxytryptamine. Showing the Percentage of the 8-Hour 5-Hydroxyindoleacetic Acid Excreted at 4 and 6 Hours, Before and During Treatment with Nialamide

Case No.	Before Nialamide		During Nialamide	
	4 Hours	6 Hours	4 Hours	6 Hours
1		78	93	96
2		89	85	93
3		86	89	99
4		78	50	61
5		92	89	93
6		88	63	97
7		80	59	82
8		93	100	100
9		54	52	81
10		92	94	94
11		82	63	89
12		95	52	52
13		81	67	78
14		87	0	30
15		85	97	98
16		83	100	100
17		95	82	89
18		91	73	87
Normals				
1		91	76	94
2		88	89	100

controls, we are left with 15 in whom the measure of 5-HIAA seems valid within the limits defined. The average fall in 5-HIAA excretion in these patients following Nialamide therapy is illustrated in Figure 1.

Although the group as a whole showed a significant reduction in 5-HIAA excretion, there was considerable variation amongst individuals. Again excluding patients 4, 12, and 14, six of the patients showed a reduction of over 50 per cent. after 2 weeks on 75 mg. Nialamide, the most extreme case having a twentyfold reduction (Case 5). Conversely, at the other end of the scale, 9 showed little change in 5-HT tolerance, nor did a further 2 weeks on 150 mg. Nialamide a day produce any greater effect in the 6 patients who were given a third tolerance test at the end of this period. In an attempt to elucidate this difference, the two groups were compared with regard to (1) dose of Nialamide (in relation

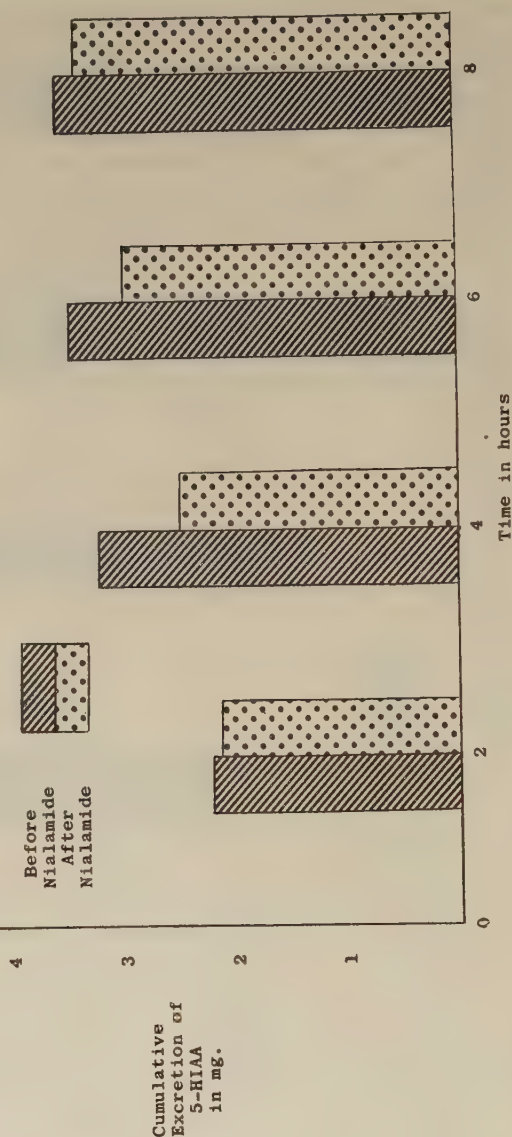
Fig. 1. Illustrating the mean urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) following oral ingestion of 10 mg. 5-hydroxy-tryptamine, in 15 subjects before and during Nialamide therapy.



to weight), (2) sex, (3) age, (4) clinical picture, (5) duration of symptoms. No distinguishing features in relation to these points were found.

None of the patients with convincing biochemical evidence of MAO inhibition showed any clinical improvement during treatment. In fact, only 2 patients (4 and 18) showed an unequivocal improvement thought to be directly due to the drug therapy (Dewhurst and Pare, 1960). In Case 4 the figures may be unreliable for the reasons given above, but in patient 18 there was no change in 5-HT metabolism as here measured (Fig. 2). Estimation of MAO activity in this case was carried out after 35 days' continuous treatment with Nialamide in an average dosage of 150 mg. a day. Subsequently, the patient relapsed on placebo and improved again when Nialamide was re-introduced, indicating that the clinical improvement was directly due to the drug therapy.

Fig. 2. Illustrating the urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) following oral ingestion of 10 mg. 5-hydroxytryptamine in subject 18 before and during Nialamide therapy.



DISCUSSION

That Nialamide inhibits MAO activity in psychiatrically normal subjects has been demonstrated by Sjoerdsma *et al.*, 1960 and the present study shows that a similar inhibition occurs in depressed patients. In two particulars, however, the results differ. Whereas Sjoerdsma *et al.*, prior to administration of an MAO inhibitor, were able to recover almost 100 per cent. of the 5-HT load as 5-HIAA, our recoveries averaged only 50 per cent., even in the normal controls. Secondly, 3 of our 20 subjects showed a definitely delayed urinary output of 5-HIAA in response to a 5-HT load when receiving Nialamide. Because of this it would seem unwise to rely on a single 8-hour specimen of

urine (Sjoerdsma *et al.*, 1958); examination of a further specimen 2-4 hours later would exclude a delayed excretion of 5-HIAA.

Another factor to be borne in mind in the interpretation of our results is that we are presumably measuring a peripheral inhibition of MAO, for 5-HT does not pass the blood brain barrier. Nevertheless, as animal experiments have shown that Nialamide can pass the blood-brain barrier after parenteral administration, to inhibit cerebral MAO, it appears legitimate to use a measure of peripheral MAO inhibition as an indicator of cerebral MAO activity. Even so, it may be that these drugs show a differential action on the different tissues and that inhibition of peripheral MAO can occur without affecting cerebral MAO or vice versa.

With these provisos in mind, it seems justifiable to conclude that inhibition of MAO does not necessarily result in clinical improvement. More important perhaps, is the indication that (in a single case) alleviation of depression by an MAO inhibitor is not necessarily associated with inhibition of MAO activity.

SUMMARY

Extracerebral monoamine oxidase activity was assessed by a 5-hydroxytryptamine tolerance test in 18 depressed patients and 2 normal controls before and after treatment with an amine oxidase inhibitor (Nialamide).

Some patients showed a considerable reduction of 5-HIAA excretion after receiving the drug but none of these showed any clinical improvement in their depression. Conversely one patient improved on the drug but showed no evidence of monoamine oxidase inhibition.

The validity of the 5-hydroxytryptamine tolerance test as an indicator of cerebral monoamine oxidase activity is discussed.

ACKNOWLEDGMENTS

We are indebted to Dr. H. Reinert of Messrs. Pfizer Ltd. who carried out the 5-HIAA estimations; to Dr. J. K. Morrison for supplies of Nialamide and to the various physicians who allowed us to study their patients.

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TRIFLUOPERAZINE ("STELAZINE") A CONTROLLED CLINICAL TRIAL IN CHRONIC SCHIZOPHRENIA

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So many new compounds are now being introduced for the treatment of psychiatric disorders that it is difficult for the clinician to assess the accuracy of the claims made for them. If a form of therapy is one hundred per cent. effective in a disease which was previously one hundred per cent. fatal, for example vitamin B₁₂ in pernicious anaemia, the question of a controlled trial does not arise. But even the manufacturers do not claim such a degree of effectiveness for drugs advocated for the treatment of mental illnesses, and in addition the natural course of such illnesses is very variable, so that it is essential that clinical trials of these drugs should be controlled. Foulds (1958) has reviewed British and American clinical trials of drugs in psychiatry during the years 1951 to 1956, and has shown that the less controlled a trial, the more likely it is to result in a favourable report on the drug being tested, presumably because of bias on the part of the clinician. Forrester (1958), however, on the basis of a completely uncontrolled trial of Stelazine on only twenty-five patients, concluded that "the amount of improvement in a few cases was not sufficient to encourage the further use of the drug".

Unfortunately, it is practically impossible to devise a perfect clinical trial in psychiatric illnesses, chiefly because of lack of precision in diagnosis. Thus, if one attempts a trial of a certain form of therapy in "schizophrenia", though great care may be taken to match groups of patients for symptoms, there is no guarantee that the underlying pathological process is the same, since the syndrome is still of unknown aetiology, and it is likely that more than one disease process can give rise to the same syndrome. Another difficulty is that it is not easy to assess the results of treatment accurately, and there is also the objection that may be made to any controlled trial, namely that it may be considered unethical to withhold treatment from the control group. This last objection carries little weight in the case of a condition such as chronic schizophrenia, in which there is as yet no treatment of proved efficacy, though a stronger case can be made in regard to depressive illness and electro-convulsive therapy.

In spite of these difficulties, however, it is clearly advisable to carry out controlled trials rather than to rely on clinical impressions, and the authors

have tried to do this in the case of trifluoperazine (Stelazine), one of the more recent additions to the list of drugs recommended for the use in psychotic and psychoneurotic disorders. It is a phenothiazine derivative, stated by the manufacturers to be about ten times as potent as chlorpromazine on a weight-for-weight basis.

Chronic schizophrenic patients in two closed wards were selected for the trial, patients over sixty years old being excluded because of the possibility of senile brain changes complicating the picture, and patients with epilepsy were also excluded because withdrawal of previous medication would not be possible. Most had received various types of therapy in the past without much effect, and the average length of time in the hospital for the patients included in the trial was 17.8 years.

All the patients were first rated on a behaviour rating sheet devised by Lucerno and Meyer (1951). The rating sheet covers eleven items of behaviour, for example, speech, psychomotor activity, attention to dress and person, toilet behaviour, and response to other patients, and there are five statements about each item, numbered from one to five. The statement most nearly fitting the patient is selected for each item, and the average of the eleven ratings is calculated. The first statement for each item indicates the most severe grade of behaviour disturbance, and the fifth indicates normal behaviour, so that the lower the final score the more marked is the deviation of the patient's behaviour from the normal. The actual assessment was made by nurses who knew the patients well.

The patients were then divided into two groups, matched as closely as possible in regard to the following characteristics: (1) age; (2) length of time in hospital; and (3) score on the behaviour rating sheet. All were males with a diagnosis of chronic schizophrenia. Out of 149 patients tested, only 24 pairs were found to be sufficiently closely matched to be included in the trial (Table I).

One member of each pair was given Stelazine tablets, and the other a placebo tablet identical in appearance but containing an inert substance. Only the hospital pharmacist knew which patient of each pair was receiving the drug. All other drugs were discontinued, apart from sedatives at night. The trial was started on Ward A with a dosage of one 5-milligramme tablet of Stelazine three times a day, but in view of the early appearance of side-effects on this dosage, when the trial on the second ward was started one week later, an initial dosage of 5 milligrammes twice a day was used, later increasing to 5 milligrammes three times a day.

ANALYSIS OF THE RESULTS OF THE TRIAL

The most appropriate statistical test for the present experimental design appeared to be a two-sample non-parametric test. This type of test is used when one wishes to determine whether treatment A exerts a more beneficial effect than treatment B, and when both individuals of a pair of patients receiving different treatments are as much alike as possible with regard to any extraneous variable which might affect the interpretation of the results. No assumptions are made with regard to normality of distribution or with regard to the scores on the scale being measured on an interval scale. The Wilcoxon Matched-Pairs Signed-Ranks Test (Siegel, 1956) is an example of this type of statistical test, and was used in this trial for the analysis of the data (scores on the behaviour rating sheet before and after treatment). Table "G" (Siegel, 1956) gives the critical values of "T" on the Wilcoxon Test for the sampling

TABLE I

Details of the Matched Pairs Prior to Treatment and Changes in Behavioural Rating Scale Scores After 6 Weeks and 3 Months of Treatment

WARD A

Pair Stelazine (S) or Placebo (P)		Age	Years in Hospital	Behavioural Rating Score		
				Before Treatment	6 Weeks After Treatment	After 3 Months of Treatment
1.	S	50	28	2.3	3.0	3.1
	P	52	30	2.4	2.54	2.0
2.	P	57	27	2.2	3.18	2.6
	S	56	26	2.0	2.45	2.1
3.	S	54	30	1.9	2.54	2.45
	P	53	30	2.1	2.54	2.0
4.	P	54	30	2.9	3.27	2.0
	S	58	27	3.1	4.0	3.7
5.	S	46	18	2.2	2.9	2.54
	P	47	16	2.2	2.09	2.4
6.	P	23	5	2.3	2.45	D
	S	22	5	2.2	3.18	3.3
7.	S	36	3	2.3	3.45	3.72
	P	37	4	2.4	3.09	3.18
8.	S	42	17	1.4	2.08	Tabs. Cancelled
	P	42	17	1.5	1.45	1.27
9.	P	P.L.*	14	2.7	3.45	3.0
	S	P.L.*	13	2.8	3.45	4.54
10.	S	54	28	1.9	1.81	1.61
	P	53	27	1.9	3.09	2.54
11.	P	50	23	1.8	1.81	2.0
		51	21	1.8	Tabs. Cancelled	Tabs. Cancelled
12.	S	P.L.	25	1.1	2.72	1.63
	P	P.L.	26	1.3	1.45	1.72

WARD B

1.	P	P.L.	43	17	2.6	2.72	2.45
	S	P.L.	48	16	2.4	2.36	Tabs. Cancelled
2.	S		55	32	1.9	1.81	1.45
	P		58	29	1.9	1.81	1.91
3.	P		33	9	1.9	1.63	Tabs. Cancelled
	S		33	11	1.9	2.36	2.36
4.	S		34	13	2.3	1.72	2.45
	P		35	11	2.4	2.27	2.54

5.	P	36	16	2.0	1.27	1.45
	S	39	18	2.0	1.09	1.81
6.	S	52	18	1.6	2.18	1.72
	P	51	18	1.5	1.36	1.45
7.	P	51	10	2.4	Refused tabs.	Refused tabs.
	S	46	11	2.3	2.09	2.54
8.	S	35	17	1.6	1.27	1.63
	P	35	17	1.5	1.45	1.54
9.	P	50	15	2.7	3.0	1.54
	S	47	13	2.6	3.0	2.45
10.	S	40	17	3.3	2.54	Tabs. Cancelled
	P	43	15	3.2	3.0	3.18
11.	P	39	10	1.7	1.9	1.54
	S	36	11	1.7	2.27	2.18
12.	S	43	12	1.9	1.81	1.9
	P	45	11	1.9	1.81	Tabs. Cancelled

* P.L. = A leucotomized patient.

distribution (the smaller sum of like signed ranks), where "N" < 25. The sum of the ranks with the less frequent sign for the six possible comparisons between Stelazine and Placebo groups, based on the mean scores of the Fergus Falls Rating Scale for both the first six weeks trial period and the three months trial period, with their levels of significance, are as follows (also see Table I for actual changes in Fergus Falls Scores for each of the pair members as treatment progresses).

TABLE II
Analysis of Fergus-Falls Behaviour Rating Scale Scores

Comparison	T.	Level of Significance
1. Stelazine and Placebo Pairs after 6 weeks		
(a) Ward A 15 (11 pairs)		Not significant
(b) Ward B 24 (9 pairs)		Not significant
(c) Ward A and B com- bined 62 (20 pairs)		Not significant
2. Stelazine and Placebo Pairs after 3 months		
(a) Ward A 10 (10 pairs)		Significant borderline .025 level
(b) Ward B 10 (7 pairs)		Not significant
(c) Ward A and B com- bined 35 (17 pairs)		Significant .025 level.

No therapeutic superiority was demonstrated for Stelazine compared with placebo after treatment covering a six weeks' period. After the trial had continued for three months, however, those patients on Stelazine, from Ward A, showed a statistically significant greater improvement than those receiving

placebo. Although this significant result was not found in Ward B the change was in the predicted direction. When the changes in the two wards were considered together a high level of statistical significance favouring the therapeutic effectiveness of Stelazine was shown.

There were four marked therapeutic successes in the trial, all four patients being on Stelazine. Three of these patients, previously suitable only for closed wards, showed such improvement that they were transferred to open wards. One of these patients, previously lazy, dirty and resistive, became co-operative and hard-working, a trusted member of one of the hospital working parties. The fourth patient had never spoken coherently and in sentences for at least the five years he had been known to the charge nurse. Under the influence of Stelazine he once again started to speak rationally and in sentences and astounded his sister when he spoke in such a way, for she had visited him for years and was used to his silence and inaccessibility at visiting times. The change in the patient was so marked that she wept.

At first glance there may appear inconsistencies between Tables I and II. These need explanation. Table I shows that there are three patients from Ward A who failed to be included in the final assessment, yet Table II shows that there were 10 pairs of patients from this ward who were included in the final analysis (Table II; 2a). This is because the data from one of these three pairs of patients was in fact included. The placebo member of the pair had deteriorated a great deal whilst his matched-pair compatriot on Stelazine had, in contrast, greatly improved. In the analysis the deterioration of the patient was recorded as "no change" and contrasted statistically with the improvement of the Stelazine patient. Precisely the same happened to pair No. 3 Ward B, this pair being included in the final analysis. These steps were taken because if a pair is matched satisfactorily and one of the pair deteriorates so much that medication has to be withdrawn, and providing the other member of the pair makes a positive response, there appears no reason why such a pair's results should be omitted. If, however, one of the pair deteriorates, necessitating cancellation of medication and the other member of the pair continues with medication, but shows either no change at all or is worse, then it would clearly be very difficult or impossible to include the results of such a pair. (There were thus 18 pairs in all who completed the trial. One pair of these had to be omitted for statistical reasons (they had identical scores).)

It is the first task of a controlled trial to demonstrate positively or otherwise the value of a preparation. After this phase has been completed and results are shown to be positive, as in this trial, the next problem is to determine those variables most closely associated with maximum therapeutic response to the drug. To this end, the Stelazine-treated patients were divided into two groups—those who had improved, and those who had got worse, and the Mann-Whitney "U" test (Siegel, 1956) was applied to the age and length of hospitalization data, to determine whether differential response to treatment was at all related to these two variables. Neither age ($P=0.3594$) nor length of hospitalization ($P=0.1401$) differentiated the "improved" or "worse" Stelazine patients.

Once the trial had been completed, the charge nurses for the two wards were asked to complete the Wittenborn Psychiatric Rating Scale (Wittenborn, 1955) for each patient in respect of his symptoms and behaviour *before* the trial began. The scores on this scale for Stelazine patients who had improved were then compared with the scores of those who had got worse. In this way it was hoped to relate response to the drug to degree and type of symptom prior to treatment. The Wittenborn Scale is graded into nine clusters of symptoms

which were isolated by factorial analysis studies. The clusters and the significance of the differences (one-tailed test) in standard cluster score values before treatment for subsequently "improved" and "worse" Stelazine patients are given in Table III. A general differentiating factor between the improved and worse patients appears to be the severity of the illness: the less severely ill on any or all of the scales appear to show the most favourable response to the drug.

TABLE III

Showing the Significance of the Differences in standard Cluster Score Values on the Wittenborn Psychiatric Rating Scale before treatment, for subsequently "Improved" and Subsequently "Worse" "Stelazine" Patients

1	2	3	4	5	6	7	8	9
Acute Anxiety	Conversion Hysteria	Manic State	Depressed State	Schizophrenic Excitement	Paranoid Condition	Paranoid Schizophrenia	Hebephrenic Schizophrenia	Phobic-Compulsive
.05	<0.01>0.001	>.05	.01	<.01	<.025	.025	<.001	<.025

SIDE-EFFECTS

Nine patients developed signs and symptoms of extrapyramidal dysfunction. They appeared to fall into two distinct groups: (1) patients who developed torticollis, oculogyric spasm, spasm of facial muscles, and tachycardia, within a day or two of the commencement of the course of Stelazine, and (2) patients who gradually developed a Parkinsonian appearance, generalized slowness of movement and excessive salivation, after about one month. There were five patients in the first group and four in the second.

The Parkinsonian syndrome of late onset appears to be similar to that which has frequently been described with chlorpromazine and other phenothiazine compounds, though excessive salivation appears to be a more prominent feature. It soon responded to reduction of dosage, without the use of anti-Parkinsonian drugs.

The syndrome of torticollis, oculogyric spasm, tremors and tachycardia occurred within a very short time of the commencement of the Stelazine course (in two cases after a total of only 25 milligrammes of the drug had been given), and the symptoms were of short duration (15 minutes to 4 hours). The term "extra-pyramidal seizures" (Paulson, 1959) aptly describes this syndrome. Though rather alarming at the time, these symptoms rapidly disappeared on reduction of dosage from 5 milligrammes three times a day to 5 milligrammes twice a day, and seemed to leave no residual effects. None of the patients on the second ward developed "extra-pyramidal seizures", indicating that it is important to begin with a low dosage and increase gradually.

One patient developed hypotension and tachycardia after a few days on Stelazine, and treatment had to be discontinued. On looking through his records, it was found that he had had the same type of reaction when receiving chlorpromazine 125 milligrammes three times daily, eighteen months previously, and this had also to be discontinued. This was presumably a case of idiosyncrasy to the phenothiazine group of drugs.

Stelazine was also discontinued in two patients after four weeks and six weeks respectively on 5 milligrammes three times daily, though in the light of later experience it was probably only necessary to lower the dosage. Two patients with Parkinsonism on 5 milligrammes three times daily soon lost these symptoms on reduction to 5 milligrammes twice daily, and on reduction to this dosage no further attacks occurred in the patients with "extra-pyramidal seizures".

One patient with post-encephalitic Parkinsonism was given Stelazine in error—his name happened to be the same as one of the schizophrenic patients who had been included in the trial—and he developed generalized weakness, so that the drug was immediately discontinued. It is interesting that these symptoms soon disappeared after withdrawal of the drug, and there seemed to be no permanent effect on his pre-existing Parkinsonism.

One patient was lost to the trial on the first day, because he adamantly refused to have any tablets at all, and two patients on placebo tablets were withdrawn from the trial because of a marked deterioration in their behaviour, possibly because of discontinuance of previous medication.

After three months, a total of seven pairs had been lost to the trial.

In the various clinical trials which have so far been published, there is great variation in the incidence of extra-pyramidal side-effects, the explanation almost certainly being that the dosage used varies considerably from trial to trial. Thus May *et al.* (1958), using 2 milligrammes three times daily in the treatment of psychoneurotic patients, reported no side-effects after one month's administration, whereas Madgwick *et al.* (1958), using 10 milligrammes three times daily, reported side-effects in 46.5 per cent. of their patients. Klimczynski (1958) gave initial doses ranging from 5 to 20 milligrammes four times daily and noted side-effects in 37 out of 48 patients, and Forrester (1958) produced Parkinsonism in 18 out of 25 patients with a dosage of 30 to 45 milligrammes daily (two to three times that used in the present trial). Side-effects appear to be uncommon in patients given not more than 10 milligrammes daily, and there appears to be a considerable individual variation in the tendency to develop side-effects on higher dosage. Rudy *et al.* (1958) gave some of their patients 100 to 300 milligrammes daily without producing any side-effects.

The fact that the five cases of "extra-pyramidal seizures" all began about $1\frac{1}{2}$ hours after the midday dose suggests that there may be some tendency to cumulation if given at too-short intervals, and administration twice a day may prove to be the better method. As mentioned above, none of the patients who were given an initial dosage of 5 milligrammes twice a day developed these symptoms, and in this connection it is interesting that Oakley (1959) found a very low incidence of side-effects when using a single daily morning dose of 10 milligrammes, gradually increasing to 40 milligrammes daily; in no case did he find it necessary to discontinue the drug. Probably both low dosage at first, with gradual increase, and spacing of doses are important for the avoidance of side-effects.

Various other side-effects have been described. for example anorexia, drowsiness, motor restlessness, and in women lactation, but none appear to be either dangerous or irreversible, and in particular there appear to have been no cases of blood dyscrasia or liver damage, in spite of the very high dosage used in some trials. Most authors report that extra-pyramidal symptoms disappear within a few days of withdrawing the drug or reducing the dosage, though some advocate continued administration of Stelazine together with drugs normally used in the treatment of Parkinsonism.

SUMMARY

A controlled trial of trifluoperazine (Stelazine) in chronic schizophrenia is reported. Analysis of the results indicates that this substance is of value in the symptomatic treatment of this condition, and that the less severely affected patients appear to benefit most from its use. Neither the age of the patient nor

the length of time in hospital seem to influence the results of treatment. It was not found possible to show that one symptom or group of symptoms responded better than another, but further investigation with larger numbers of patients might yield results in this respect, and would be of value in leading to more precise indications for the use of this drug.

Side-effects, mainly in the form of extra-pyramidal dysfunction, were fairly common but tended to disappear on reduction of dosage; they were not considered to be a serious disadvantage of the drug, and should seldom necessitate discontinuation of treatment. The incidence of side-effects can be reduced by commencing with a small dose and then gradually increasing, and probably also by using twice daily rather than thrice daily administration.

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UNEVENTFUL TRIFLUOPERAZINE (STELAZINE) THERAPY AFTER PREVIOUS GRANULOCYTIC DEPRESSION

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THERE are many reports referring to incidence of agranulocytosis in patients receiving phenothiazines. This and the potential hepatotoxic effect of this group of drugs have been the greatest drawback in their usage.

For this reason it is felt worth while reporting the following case, not only because it is to the author's knowledge the first case of white cell depression concomitant with administration of trifluoperazine, but also because it demonstrates the usefulness of routine haematology, particularly in the initial stages of treatment with a new medication. In addition the reinstitution of therapy with trifluoperazine resulting in much improved mental status with no toxic bone marrow effects is of interest.

G.C., a 34-year-old catatonic schizophrenic, extremely regressed, mute, refusing to wear clothes and incontinent, was placed on perphenazine (Trilafon (Schering, perphenazine)), eventually reaching a dosage of 48 mg. per day (he received perphenazine for 20 weeks with some slight improvement only). On 3 March, perphenazine was discontinued and he was put on trifluoperazine, 10 mg. t.i.d. Within three days some improvement was noted and at the end of a week he was fully dressed, talking and able to feed himself. However, by 16 March, a diminished granulocyte count was evident (see accompanying table). Because of the frequency of low white cell count on patients receiving medication, he was carefully watched and the medication continued. However, by 31 March a serious white cell depression was evident and he was withdrawn from the medication and for prophylactic purposes procaine penicillin, 1 million units daily, instituted for eight days. Blood counts were taken daily and within five days the haematological picture was normal for this patient. His mental state again relapsed, he was no longer clothed, feeding himself nor continent. He was then placed on reserpine, 10 mg. per day, by injection (he refused oral medication). One week later this was reduced to 5 mg. per day, combined with 2 mg., b.i.d. Cogentin. He improved to the stage of remaining dressed, but was bizarre, silly, grimacing and with inappropriate affect. He was sexually aggressive and quite uninhibited. The reserpine-induced salivation resulted in his continually spitting, occasionally in the faces of the nurses and doctor. On 24 April, it was decided to withdraw the reserpine and again administer trifluoperazine, 30 mg. per day as previously. This decision was made because of his poor response to medications other than trifluoperazine. Daily white cell counts were taken and the patient closely observed. The patient slowly improved and after three weeks of treatment was no longer bizarre, aggressive nor inappropriate, was fully clothed and ate well. After ten weeks of treatment he was accepted for

a home visit and although this visit was unsuccessful this did represent his first time out of the hospital in twenty months.

TABLE I

Date	W.C.C.	P.	E.	L.	M.	
2.3.60	5,400	71	4	23	2	
Trifluoperazine commenced						
9.3.60	6,400	65	2	32	1	
16.3.60	3,800	57	2	39	2	
24.3.60	4,000	56	6	35	3	
31.3.60	2,800	53	2	42	3	
Trifluoperazine withdrawn						
1.4.60	3,600	55	3	38	4	
2.4.60	3,200	52	6	42	—	
3.4.60	4,700	70	3	26	—	
4.4.60	3,800	58	6	34	2	
5.4.60	4,400	57	7	34	2	
6.4.60	6,700	72	2	24	3	
7.4.60	4,500	56	2	38	4	
8.4.60	7,200	64	4	31	1	
11.4.60	5,600	69	3	27	1	
13.4.60	6,500	64	4	30	2	
19.4.60	6,400	71	1	28	1	

W.C.C.—Total white cell count.

P.—Polymorph leucocytes.

E.—Eosinophils.

L.—Lymphocytes.

M.—Monocytes.

All bloods were taken at the same time each day, the only exception being the one on 8.4.60.

DISCUSSION

Phenothiazines are potent, extremely useful therapeutic agents in the management of many conditions. The presence of the nitrogen-benzene linkage places it in Damshek's category of "white cell granulocyte reactors" (1). The occurrence of a depressed white cell count whilst receiving trifluoperazine is, therefore, not surprising. The failure to reproduce a leukopenic reaction on reinstitution of the drug does not at all exclude this as a causative agent. Yules *et al.* (2), Platter *et al.* (3), Jacoby (4), Pisciotta *et al.* (5), have all reported cases of agranulocytosis resulting from chlorpromazine therapy, which did not recur on re-administration of chlorpromazine.

On the other hand, Pisciotta reports cases where agranulocytosis did recur whilst in Jacoby's reported case the patient had had two attacks of agranulocytosis before receiving 6,400 mg. daily of chlorpromazine for four months without any ill effect.

The frequency of occurrence of agranulocytosis during chlorpromazine therapy is estimated at 0.001 to 0.002 per cent. (6). The widespread usage and low toxicity of this agent has made the use of routine blood counts fall into disfavour. The importance of infection as a danger signal seems to be likewise ignored; this latter seems an unnecessarily dangerous situation. Particularly in a new medication it is felt that the former is a careful choice, the latter obligatory. Pisciotta, in discussing eighteen cases of agranulocytosis due to chlorpromazine, states that nine were detected on routine blood checks and nine because of infection.

The question of dosage, time and rapidity of onset of agranulocytosis

is frequently raised. The Pisciotta article claims that phenothiazines produce a toxic effect similar to antithyroid drugs, that is, rarely before the tenth day of administration; the onset is gradual and only after large dosages are given. This, they assume, is due to an increasing concentration of the drug in the bone marrow. This latter statement seems doubtful and is based mainly on the fact that most cases of agranulocytosis have been reported in psychiatric patients where higher dosages are usually employed (in effect mental hospitals). The case here reported received the same high dosage on both occasions and Jacoby's case received enormous quantities of chlorpromazine after previously exhibiting white cell depletion on two occasions. It seems equally possible that a metabolic factor could be involved either due to poor nutrition or associated with schizophrenia. If this were so, one could hypothesize that in the case reported here the initial good response to trifluoperazine, resulting in normalized activity, including dietetic, may have had a protective role when the drug was readministered.

SUMMARY

1. A case is presented of granulocytic depression reaching serious proportions in a patient receiving trifluoperazine, which subsequently reached normal levels when the drug was discontinued.
2. Readministering the drug at a later date again resulted in improvement of the patient's condition but no evidence of toxic effect on the bone marrow was noted.
3. The value of routine white cell counts on patients receiving phenothiazines is again emphasized.
4. Possible factors in causing agranulocytosis are briefly discussed.
5. Even in a single case, the therapeutic efficacy of trifluoperazine is demonstrated.

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A CHROMATOGRAPHIC STUDY OF THE AMINO ACIDS IN URINE AND C.S.F. FROM MENTALLY DEFICIENT CHILDREN

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INTRODUCTION

As a result of new methods of biochemical investigation an increasing although yet small number of cases of mental deficiency can be shown to be caused by congenital metabolic abnormalities. In 1958 Wright *et al.*, reviewed and classified anomalies of this nature and since then a new syndrome has been described by Allan *et al.* (1958) and a syndrome closely related to, if not identical with, Maple Syrup Urine Disease by Smith and Strang (1958).

Urine chromatography is now a recognized part of the investigation of mental deficiency but although it is known that the same abnormality may be present in both urine and C.S.F. as in Allan's cases and in Maple Syrup Urine Disease (McKenzie and Woolf, 1959), it is not clear whether C.S.F. chromatography is indicated where the urine chromatogram shows none of the known syndromes. In the present study the amino acids of both urine and C.S.F. from a number of mentally defective patients have been investigated by paper chromatography.

CASE MATERIAL

Forty patients were studied (25 male and 15 female), their ages ranging from 18 months to 21 years with most being in middle or late childhood. Thirty-two of the cases were accommodated in a mental deficiency Institution and intelligence testing had been carried out on practically all of these, showing that they fell into the imbecile or idiot categories of mental defect. The remaining eight cases were in-patients in a paediatric medical ward for various reasons, and were considered on general observation to have a gross degree of mental defect. As far as possible, only cases of primary oligophrenia were included, but in a few instances accurate information was not available about the

perinatal period and this may have permitted the inclusion of an occasional patient who had suffered from birth injury, anoxia or other influence.

METHODS

Urine. One random specimen was obtained in each case. It was preserved with thymol and kept in a refrigerator. Each specimen was tested by qualitative chemical methods for protein, glucose, sucrose, cystine and phenylpyruvic acid. Total nitrogen was determined by Conway's microdiffusion method following Kjeldahl digestion of the urine.

The free amino acids were investigated by two-dimensional chromatography on Whatman No. 4 paper sheets 11 inches $\times$ 18 inches. The volume of urine used was that which contained 500 μ g. total nitrogen. This received no preliminary treatment before being applied to the paper except in several cases where salt distortion interfered with the definition of the spots on the finished chromatogram. In these cases the chromatograms were repeated after de-salting the required volumes of urine with Zeocarb 225 cation exchange resin.

The first solvent used was Phenol : m-Cresol : Water = 20 : 20 : 9 in the presence of ammonium hydroxide and potassium cyanide. This was run upwards overnight over the shorter dimension of the paper. The second solvent was n-Butanol : Glacial Acetic Acid : Water = 50 : 11 : 25 run downwards overnight off the paper until Leucine came to about 3 inches from the bottom edge.

The dried papers were sprayed with a fresh mixture of 1 per cent. ethanolic ninhydrin, 2 : 6 lutidine and glacial acetic acid in the proportions 50 : 3 : 15. The coloured spots were developed in a heated fume-cupboard at about 50° C. The intensities of the spots were assessed visually on an arbitrary scale of 5 units on which 1 represented a faint but definable spot and 5 a strong well-defined spot. Quite often indefinable shadowy spots were seen which have been evaluated as "trace" and occasionally very strong spots evaluated as >5 . The corresponding values in terms of micrograms of amino acid were assessed by carrying out a series of chromatograms using standard solutions of the individual amino acids.

Cerebro-spinal fluid. One specimen was obtained by lumbar puncture in each case. Cell count, total protein estimation, globulin estimation and Wassermann reaction were carried out on each specimen.

The free amino acids were investigated chromatographically as in the urines. The volume of C.S.F. used (1 ml.) was prepared for chromatography by the method of Prior and Whitehead (1953) in which the specimen is simultaneously deproteinized and de-salted on a column of Zeocarb 225 resin.

RESULTS

Urine. Protein, glucose, sucrose, cystine and phenylpyruvic acid were not detected in any of the specimens by the qualitative tests used.

The volumes of urine required for chromatography ranged from 45 μ l. to 195 μ l., most being between 70 and 100 μ l.

Table I shows the total number of amino acids found on each urine chromatogram. From 3 up to 15 spots were seen per paper.

In Table II, the 17 individual amino acids which were found are listed according to the frequency of their occurrence. The intensity of each spot is also recorded along with an indication of the approximate amount of amino acid required to give that intensity under the conditions used.

TABLE I
Number of Amino Acids Found on Each Urine Chromatogram

No. of Amino Acids	No. of Chromatograms
3	1
4	2
5	1
6	3
7	2
8	11
9	4
10	3
11	2
12	4
13	2
14	2
15	3

TABLE II
The Frequency of Occurrence and Spot Intensities of the 17 Amino Acids Found on Urine Chromatograms

			Occurrence on 40 Chromatograms					
Amino Acid	Times Found		No. of Times at Different Spot Intensities					
	No.	Per cent	Trace	1	2	3	4	5
Glycine ..	40	100	—	1 (1)	14 (4)	14 (7)	9 (12)	2 (17)
Alanine ..	40	100	1 (1)	13 (2)	17 (4)	5 (7)	3 (9)	1 (12)
Histidine ..	38	95	—	7 (5)	13 (10)	12 (20)	5 (30)	1 (40)
Serine ..	37	92	3 (<1)	10 (1)	11 (3)	9 (6)	2 (10)	2 (15)
Glutamine ..	35	88	1 (5)	14 (10)	13 (15)	4 (25)	2 (45)	1 (65)
Threonine ..	28	70	1 (<1)	15 (1)	9 (3)	3 (6)	—	—
Ethanolamine ..	27	67	6 (<1)	11 (<1)	10 (1)	—	—	—
Glutamic Acid	26	65	2 (1)	8 (1)	9 (2)	5 (4)	2 (7)	—
Tyrosine ..	22	55	8 (3)	9 (5)	5 (10)	—	—	—
Leucine ..	13	33	4 (1)	3 (4)	6 (6)	—	—	—
Valine ..	13	33	6 (1)	5 (2)	2 (4)	—	—	—
Taurine ..	11	27	—	—	7 (6)	4 (12)	—	—
Histamine ..	11	27	3 (4)	6 (7)	1 (12)	1 (17)	—	—
Aspartic Acid ..	9	23	1 (<1)	3 (1)	3 (3)	2 (6)	—	—
Lysine ..	8	20	—	1 (5)	5 (8)	2 (12)	—	—
Arginine ..	8	20	1 (3)	2 (6)	4 (10)	1 (15)	—	—
β amino iso-butyric Acid	5	13	—	4 (7)	—	1 (16)	—	—

The figures in brackets indicate the approximate amounts (μ g.) of the individual amino acids required to produce the various spot intensities.

Cerebro-spinal fluid. The results of the routine determinations of cells, total protein and globulin were within the normal ranges. The Wassermann reaction was negative in each case.

Table III shows the total number of amino acids found on each C.S.F. chromatogram. From 3 up to 11 spots were seen per paper.

TABLE III
Number of Amino Acids Found on Each C.S.F. Chromatogram

No. of Amino Acids	No. of Chromatograms
3	2
4	4
5	2
6	8
7	9
8	4
9	5
10	3
11	3

The frequency of occurrence and spot intensities of the 13 individual amino acids found are shown in Table IV.

TABLE IV
The Frequency of Occurrence and Spot Intensities of the 13 Amino Acids Found on C.S.F. Chromatograms

			Occurrence on 40 Chromatograms						
Amino Acid	Times Found		No. of Times at Different Spot Intensities						
	No.	Per cent.	Trace	1	2	3	4	5	>5
Glutamic Acid	40	100	—	—	2	4	7	23	4
Glutamine ..	40	100	—	2	3	15	10	9	1
Alanine ..	37	93	3	13	15	5	1		
Glycine ..	36	90	1	6	21	6	2		
Leucine ..	33	83	3	15	11	3	1		
Threonine ..	28	70	4	19	4	1	—		
Valine ..	22	55	4	13	4	1	—		
Serine ..	13	33	—	2	6	3	2		
Tyrosine ..	13	33	6	7	—	—			
Aspartic Acid	9	23	2	4	1	2			
Histidine ..	8	20	1	2	4	1			
Arginine ..	2	5	—	2					
Lysine ..	2	5	—	2					

DISCUSSION

Urine. Under the conditions used it is generally found that a volume of a normal child's urine containing 500 μ g. total nitrogen shows on chromatography about 5 to 8 amino acid spots. These are usually Glycine (3)*, Alanine (3), Histidine (3), Serine (3), Glutamine (2), with sometimes Glutamic Acid, Threonine and Taurine. The relative amounts of Glutamine and Glutamic Acid depend on how long the urine has been kept, Glutamine giving rise to Glutamic Acid which is virtually absent from freshly voided urine (Stein, 1953).

* Numbers refer to spot intensities.

Seventeen of the forty urine specimens from the mental defectives gave findings in this range of 5 to 8 spots. Three specimens showed fewer amino acids: one of these gave a spot of medium intensity for Glycine along with faint spots for Alanine and Glutamine. The other two were the same with the addition of a faint spot for Histidine. The remaining twenty urine chromatograms showed from 9 to 15 spots. The patterns were composed basically of the 6 most commonly occurring amino acids present at normal concentrations accompanied by some of the less common amino acids at rather low concentrations. Details of the frequency with which the individual amino acids occurred may be seen in Table II.

Cerebro-spinal fluid. No C.S.F. specimens were obtained from mentally normal children so that the C.S.F. findings can be compared only with normal chromatographic results given in the literature.

In three specimens of normal C.S.F. (0.625 ml.) Walshe (1953) found Glutamine as the dominant spot with faint spots of Glycine, Serine, Alanine, Glutamic Acid, Valine and Leucine. Schöenberg (1954), using 0.5 ml. normal C.S.F., reported the presence of Glutamine, Glutamic Acid and small concentrations of Valine and Leucine. Walker *et al.* (1955) investigated twenty-six C.S.F. specimens from normal patients. He listed the number of times that each of 18 amino acids was found and also gave the concentrations of the 11 most common. The volume of fluid used is not stated. Using 1 ml. C.S.F. Logothetis (1955) identified 15 amino acids in seventeen normal specimens. He gives the percentage occurrence of each amino acid and also the concentration as determined by colour density readings on the chromatograms.

Compared with these results the forty C.S.F. specimens in this series show the same prominent amino acids—Glutamine, Glutamic Acid, Alanine, Glycine, Leucine, Valine and Threonine. As in the urine Glutamine and Glutamic Acid may be considered together (Ludewig, 1953). Altogether 13 different amino acids were found.

The main difference between the figures in Table IV and the normals of Logothetis is in the occurrence of Aspartic Acid, Serine, Tyrosine, Lysine and Histidine. The first 4 of these were found much more frequently by Logothetis than in the present series. Histidine, which was identified on eight of our papers, was not found by Logothetis in the C.S.F. of mentally normal persons. He did, however, identify it in the specimens from mentally abnormal patients.

Walker also detected Aspartic Acid, Serine, and Tyrosine on almost all of his chromatograms of normal C.S.F. but Lysine on only 15 per cent. He noted Histidine on 54 per cent. of his normals.

Urine and Cerebro-spinal Fluid. No unidentified spots were found on the urine or C.S.F. chromatograms and there was no amino acid present in excessively high concentration. Moreover, the less common amino acids were never found in the absence of the common ones.

A comparison was made for each patient of the number of amino acid spots found in the urine and the number found in the C.S.F. On any paper a number of spots are very faint (intensity 1) or mere traces and it was decided to include in this particular comparison only well-defined spots of intensity 2 or more units. Considering only these, we have divided all the chromatograms into three groups—high, middle and low—according to the number of spots present.

The middle group of urine chromatograms is taken as those containing 3 up to 6 amino acid spots of intensity 2 or more which is the range usually found here in the urine of normal children. Eighteen papers fall into this group

while six show fewer than 3 spots (low group) and sixteen show from 7 up to 12 spots (high group).

As mentioned previously, we had no normal C.S.F. specimens so a table was drawn up corresponding to Table III but showing only amino acid spots of intensity 2 or more units. It was then found that almost half (nineteen) of the forty C.S.F. chromatograms showed either 3 or 4 spots. These nineteen were taken as the middle group. There were five C.S.F. papers with fewer than 3 spots of intensity 2 or over (low group) and sixteen with from 5 up to 9 spots (high group).

The comparison of urine and C.S.F. specimens is summarized in Table V which shows a moderate degree of correlation especially in the specimens with high amino-acid content where ten of the sixteen urines are from patients whose C.S.F. specimens also show high amino acid content. Similarly, of the eighteen urines in the middle group twelve have C.S.F. findings in the corresponding range.

TABLE V

Comparison of Amino Acid Content of Urine and C.S.F. Chromatogram from Individual Patients

(Spots of Intensity 2 or over)

	No. of Urines in Each Amino Acid Group		
	Low Group (<3 Spots)	Middle Group (3-6 Spots)	High Group (>6 Spots)
No. of C.S.F.s in each Amino Acid Group:			
Low Group (<3 spots)	 2	1	2
Middle Group (3-4 spots)	 3	12	4
High Group (>4 spots)	 1	5	10

No amino acid was present in exceptionally high concentration and basically the amino acid pattern of urine differs from that of C.S.F. so that it was not feasible to compare the occurrence and concentration of individual amino acids in the two fluids.

An attempt was made to correlate features from the patients' case histories with the urine and C.S.F. findings but specific clinical traits were so uncommon in these cases of primary oligophrenia that no information of value was obtained.

SUMMARY

A chromatographic study was made of the amino acids present in the urine and C.S.F. of forty mental defectives aged from 18 months to 21 years, most being in middle or late childhood. Some of the patients showed a moderate degree of aminoaciduria and these patients tended also to have the highest numbers of amino acids in the C.S.F. chromatograms.

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PSYCHIATRIC ILLNESS IN ADOLESCENCE: PRESENTATION AND PROGNOSIS

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INTRODUCTION

A UNIT for adolescent psychiatric patients was opened at St. Ebba's Hospital in 1949 by the late Dr. D. E. Sands. At that time, there were few in-patient facilities for this group of patients and the unit therefore received many of the most disabled cases from all parts of the country. Sands (1953)* wrote of the need for such a unit. "In the juvenile period there is psychiatric breakdown to a degree which from medical and social standpoints is as much of a problem as such illness in later life. There are some who have stated that all children's and juvenile psychoses should be treated at home. Experience with these patients has shown that, however desirable this may be in theory, it is no more practical or safe for some types of juveniles than for adults. The truth of this view might have been inferred in any case from the frequency with which such cases have found their way for years into all kinds of makeshift in-patient accommodation because home for one reason or another proved impossible or practically non-existent". He then gave an account of the classification, aetiology and treatment of patients on the unit and the results on discharge. The present article discusses the presentation of psychiatric illness in adolescence, reviews the follow-up on patients admitted between 1949 and 1953 and compares these follow-up results with those of Sands on discharge.

The unit has 30 male and 30 female beds and a school, run by the local education authority, is attached to it. The ages of the patients have ranged between seven and eighteen years but the majority are over twelve. They are referred from child guidance clinics, psychiatric out-patients, juvenile courts, special schools and remand homes. They therefore form a selected group of patients, who are too incapacitated to be treated at home or in various institutions.

Patients suffering from irreversible organic states have been excluded from this survey. These conditions consisted mainly of epilepsy without psychiatric disorder, post-encephalitic states and severe subnormality. This has left 362 patients, who have been followed up for a period of two to five years.

The diagnostic categories are shown in Table I. Over half the patients came into the group of behaviour disorders. This term has been used in preference to psychopathic reaction as the diagnosis of psychopath suggests a poor prognosis which should not be assumed in the developing adolescent. The main symptoms shown by these patients are violence, stealing, truancy and sexual disorders. About a quarter of the patients suffered from schizophrenia, contrasting with the rarity of affective disorders in this age group. The remainder presented with neuroses, of which the least common were obsessional states.

* Sands, D. E., *J. Ment. Sci.*, 1953, **414**, 123.

TABLE I

Diagnosis				Male	Female	Total	Percentage Total
Behaviour disorder	..	..	..	131	67	198	55
Schizophrenia	..	..	..	39	39	78	22
Anxiety state	..	..	..	25	8	33	9
Hysteria	..	..	..	14	16	30	8
Affective disorder	..	..	..	13	2	15	4
Obsessional state	..	..	..	6	2	8	2
Total	..	..	..	228	134	362	

Table II summarizes the condition at discharge of each diagnostic category. Affective disorders and obsessional states have a favourable outcome in this age group. Neuroses and behaviour disorders occupy an intermediate position, the prognosis of a psychopathic reaction in adolescence being far better than in the adult. In contrast, schizophrenia has a worse prognosis than in the adult where recovery can be expected in a third of patients.

TABLE II

Diagnosis				Recovered (Per cent.)	Improved (Per cent.)	No Change (Per cent.)	Worse (Per cent.)
Behaviour disorder	..	..	..	38	22	37	3
Schizophrenia	..	..	..	19	23	58	—
Anxiety state	..	..	..	55	24	6	15
Hysteria	..	..	..	40	43	7	10
Affective disorder	..	..	..	80	13	7	—
Obsessional state	..	..	..	50	50	—	—

Table III shows that psychiatric illness was commoner in eldest children and that only children were not at particular risk.

TABLE III

Eldest	Middle	Youngest	Only	Not Known
109	80	80	83	10

Table IV illustrates the relationship of a stable home or stable institutional background to each diagnostic category. Patients with behaviour disorders were more liable to have unstable homes. This may be a reflection of environmental or hereditary factors or the two combined. Although psychoanalytic theories often postulate a disturbance in early family relationships as a cause of schizophrenia, this was not apparent in this survey. Those with affective disorders and obsessional states usually had a stable home background.

TABLE IV

Diagnosis						Background	
						Stable	Unstable
Behaviour disorder	..	..	..	..	..	83	115
Schizophrenia	..	..	..	..	..	51	27
Anxiety state	..	..	..	..	..	21	12
Hysteria	..	..	..	..	..	16	14
Affective disorder	..	..	..	..	..	13	2
Obsessional state	..	..	..	..	..	7	1

Each diagnostic category will now be considered in relation to presenting symptoms and factors affecting prognosis.

BEHAVIOUR DISORDER

This forms a miscellaneous group of psychiatric disorders in the adolescent. Its incidence is comparatively high, as adolescents are more outgoing and tend to externalize their problems in a "social neurosis". Adults are more prone to internalize their conflicts and express them in the form of a conversion hysteria, generalized anxiety or anxiety transformed into somatic manifestations. The following two cases illustrate one type of behaviour disorder, which may be constitutional in origin and produce the adult psychopath.

Case 1—A girl, aged 16, was admitted from an approved school after threatening to strangle people and killing the school cat.

Her father was unstable and callous. A maternal grandmother had served a prison sentence for manslaughter. Her father's viciousness made the home a very disturbed one and her parents separated a year before her admission. She was always in trouble at school but passed the 11+ examination and went on to a grammar school from which she was expelled after a year for truancy. She adjusted no better at a comprehensive school.

She started prostitution at 13 and began work in a night club as soon as she left school. She sometimes earned forty pounds a week and could see no incentive to change her way of life, which suited her temperament. She enjoyed prostitution as a means of degrading men and only obtained sexual gratification in relations with women under the age of thirty. She was addicted to Preludin. She intended to live until the age of 25 when she would commit suicide.

She was sent to an approved school after being picked up in a police raid on the club. She had no wish for treatment and soon absconded.

Case 2—A girl, aged 16, was referred for persistent truancy. She was an illegitimate child of a schizophrenic mother. She had been in three institutions, started to steal and play truant at the age of 14 and the episodes became more frequent. She absconded from the hospital about once a fortnight and there was rarely any discernible cause. She allowed herself to be picked up by lorry drivers and would then go to the police and accuse them of assault. Her conduct was not influenced by firm or permissive handling, she always blamed others and told fantastic stories. She had to be placed under permanent institutional care.

In contrast, the following two cases show that disordered behaviour may be the equivalent of a neurotic reaction to situations of severe stress.

Case 3—A girl, aged 16, was referred with a history of stealing and promiscuity.

Her parents were strict, respectable, orthodox Jews. Her brother conformed to the family ideals and was always held up as an example to her. Her parents were well suited but there was an antagonism between herself and her mother from early childhood. She made an average adjustment to school until her last years when she occasionally played truant. She then had four jobs in quick succession until settling down as a telephonist.

The incompatibility with her mother and the contrast between the ideals of her teen-age contemporaries and her strict home led her to associate with local delinquent society as a form of rebellion. She became promiscuous with the intention of spiting her mother and got into trouble after stealing forty pounds to pay off the fine of her boy friend.

She made genuine attempts to meet her parents half-way but the incompatibility proved insoluble on both sides and she was finally placed with an aunt who was tolerant of her adolescent ideas and dress.

Case 4—A girl, aged 14, was referred for truancy from school.

Her mother was placid and sympathetic. Her father had been nervy for some time. She was an only child. The home was stable and the girl's adjustment satisfactory until the age of ten when her father, who was a teacher, obtained a job in Cyprus. They changed house four times, lived under the strain of guerilla warfare and her parents began to quarrel. Her father started an association with a local girl with the tacit consent of her mother, who felt it would be good for his nerves. In addition, the patient had to adjust to a school where most of the pupils were Greek and much of the teaching was in that language.

She showed disturbed behaviour soon after arrival in Cyprus. She shut herself in cupboards at school or truanted and hid in the country. At other times, she associated with soldiers and was often picked up by the military police. The crisis came when she complained to the school authorities that her father had tried to have relations with her and he lost his job.

She returned to England with her mother and her disturbed behaviour gradually subsided after a period in hospital.

These four patients show the type of case placed in the category of behaviour disorder. Prognostic factors will now be considered in more detail. Table V gives the prognosis and duration of follow-up in this group of patients. It will be seen that 60 per cent. are recovered or improved after a follow-up of two to five years. Six of the patients were estimated as being worse. Two male patients developed schizophrenia, showing that this disease is a rare sequel to a behaviour disorder. One male patient was charged with transvestism and one female patient with prostitution. One female patient was in Broadmoor for murder and another had been charged with attempted murder.

TABLE V

Follow-up in Years	Sex		Recovered	Improved	No Change	Worse	Total
Two	Male ..	..	7	4	3	0	19
	Female ..	..	1	1	2	1	
Three	Male ..	..	9	6	6	0	40
	Female ..	..	5	5	9	0	
Four	Male ..	..	8	4	13	1	44
	Female ..	..	6	5	6	1	
Five	Male ..	..	30	14	24	2	95
	Female ..	..	10	4	10	1	
Total	..	..	76 (38%)	43 (22%)	73 (37%)	6 (3%)	

The prognosis was slightly improved by a negative family history, but the difference was too small to be significant. This is shown in Table VI.

TABLE VI

Family History	Recovered	Improved	No Change	Worse	Total
Positive	33 (36%)	17 (19%)	38 (42%)	3 (3%)	91
Negative	43 (40%)	27 (25%)	34 (32%)	3 (3%)	107

Similarly, although the prognosis was a little better with a stable home or institutional background, the difference was not significant when recovered and improved cases are combined.

TABLE VII

Background	Recovered	Improved	No Change	Worse	Total
Stable	40 (48%)	15 (18%)	26 (32%)	2 (2%)	83
Unstable	36 (31%)	29 (25%)	46 (40%)	4 (4%)	115

Table VIII shows no marked difference in prognosis between the sexes.

TABLE VIII

Sex	Recovered	Improved	No Change	Worse	Total
Male	54 (41%)	29 (22%)	45 (34%)	3 (3%)	131
Female	22 (33%)	15 (22%)	27 (40%)	3 (5%)	67

The duration of hospitalization averaged five months and the outcome showed no relation to the length of stay. The prognosis was worse in patients of low intelligence. The test used in this study was mainly the Wechsler I.

TABLE IX

I.Q.	Recovered	Improved	No Change	Worse	Total
Under 80 ..	8	7	11	1	27
80-100 ..	26	22	35	3	86
100-120 ..	25	9	18	1	53
Over 120 ..	4	2	3	0	9

EEG findings have been classed as stable, non-specific unstable and epileptic. There was no marked difference in prognosis between the first two, but an epileptic record was more often associated with a poor outcome.

TABLE X

EEG	Recovered	Improved	No Change	Worse	Total
Stable	28	17	25	1	71
Non-specific unstable	38	21	31	4	94
Epileptic	5	1	6	0	12

The clearest guide to prognosis was the symptomatology, which has been categorized under the five headings of stealing, violence, truancy, sexual disorders and pyromania. Stealing and pyromania as isolated symptoms had an excellent prognosis. In contrast, the combination of stealing, violence and truancy in the same patient indicated a very poor outcome. This is shown in Table XI which gives the various symptom combinations.

TABLE XI

Symptoms	Recovered	Improved	No Change	Worse	Total
Stealing	10	3	1	0	14
Violence	20	12	14	0	46
Truancy	2	12	14	0	28
Pyromania	3	0	1	0	4
Sexual disorders ..	6	5	10	2	23
Stealing, violence ..	11	6	9	2	28
Stealing, truancy ..	5	9	10	0	24
Violence, truancy ..	12	6	9	1	28
Stealing, violence, truancy	7	2	18	0	27

SCHIZOPHRENIA

There is no difference in the presentation of schizophrenia in adolescence. It may commence with a simple, catatonic, hebephrenic or paranoid picture as in the adult. The following three cases illustrate this.

Case 5—A girl, aged 11, was referred because of excessive shyness.

Her mother had been treated for depression. The family history was otherwise negative. She walked at 15 months, talked at 18 months. She was always shy but coped satisfactorily at her primary school. On transfer to a secondary school, she gradually became mute and refused to take any part in school activities. She remained almost mute with adults but would talk to some of the other patients and did simple lessons if allowed to work at her own pace. It was later possible to treat her as a day patient.

Case 6—A girl, aged 12, had been deluded for a year.

Her father's mother was paranoid. The family history was otherwise negative. She was late in walking at two years. She was a shy child who did not mix. She made an average adjustment at school until the onset of her illness.

Her delusions started at the age of 11. She was tense, suspicious, believed her food was being poisoned and thought a neighbour had told the police her parents were going to murder

her. She heard people in the street saying she was going to die. She was admitted when she became uncontrollable at home, with a diagnosis of paranoid schizophrenia.

Case 7—A girl, aged 14, was referred because of increasing withdrawal.

The family history was negative. Her home background was stable and affectionate and her early development normal. She was a very shy child. She adjusted to primary school but broke down at her secondary school after being falsely accused of pilfering. She became increasingly solitary and withdrawn. She was manneristic, giggled to herself and, on occasion, attempted to injure herself. She presented a classical hebephrenic picture.

Table XII gives details of the duration of follow-up and prognosis in this group of 78 patients. The category of "worse" has been omitted because of the intrinsic seriousness of this illness. Recovered patients have no symptoms of schizophrenia. Improved patients have residual symptoms but are making an adequate social adjustment and are fully employed. Those unchanged are either in hospital or unemployed at home with gross psychotic symptoms.

TABLE XII

Follow-up in Years	Sex	Recovered	Improved	No Change	Total
Two	Male	1	0	4	11
	Female	1	2	3	
Three	Male	3	1	5	19
	Female	2	4	4	
Four	Male	0	3	7	20
	Female	2	2	6	
Five	Male	1	2	12	28
	Female	5	4	4	
Total		15 (19%)	18 (23%)	45 (58%)	78

Table XIII summarizes the relation of family history to prognosis. Unexpectedly, there were proportionately more recoveries in patients with a positive family history of mental illness. But when recovered and improved patients are combined there is no significant difference. Therefore hereditary factors are not a guide to prognosis.

TABLE XIII

Family History	Recovered	Improved	No Change	Total
Positive	7	3	18 (64%)	28
Negative	8	15	27 (54%)	50

The general prognosis was better in patients with a stable background but the number of recoveries was proportionately the same in each group.

TABLE XIV

Background	Recovered	Improved	No Change	Total
Stable	10	15	26 (51%)	51
Unstable	5	3	19 (70%)	27

There was a striking correlation between sex and prognosis in adolescent schizophrenia. Twice as many females recovered or improved in this series.

TABLE XV

Sex	Recovered	Improved	No Change	Total
Male	5	6	28	39
Female	10	12	17	39

The duration of hospital stay averaged nine months. As might be expected, the prognosis was best in patients with a short stay in hospital. Recovered and improved patients stayed for an average of six months while the unchanged patients averaged fifteen months. As with behaviour disorders, the prognosis was worse in those of low intelligence. This is summarized in Table XVI.

TABLE XVI

I.Q.	Recovered	Improved	No Change	Total
Under 80	0	4	12	16
80-100	6	1	11	18
100-120	4	4	4	12
Over 120	1	1	1	3

In cases where an EEG was done, recovery was favoured by a stable record.

TABLE XVII

EEG	Recovered	Improved	No Change	Total
Stable	5	4	11	20
Non-specific unstable	2	6	20	28
Epileptic	0	0	2	2

The standard treatment for schizophrenia during the period under review was deep insulin therapy. There was no significant difference in the results with deep insulin compared with those treated by psychotherapy alone and this treatment is no longer given on the adolescent unit. The prognosis was not influenced by any particular form of treatment.

TABLE XVIII

Treatment	Recovered	Improved	No Change	Total
Phenothiazines ..	1	0	3	4
E.C.T.	1	0	3	4
Leucotomy	1	0	3	4
Psychotherapy alone ..	5 (25%)	4 (20%)	11 (55%)	20
Deep insulin therapy ..	7 (15%)	14 (30%)	25 (55%)	46
Total	15 (19%)	18 (23%)	45 (58%)	78

In summary, the prognosis tended to be better in patients with a stable background, high intelligence and stable EEG record. But the only factor having a striking effect on prognosis was sex, there being twice as many remissions in female adolescents.

ANXIETY STATE

Adolescents with anxiety states tend to have the same symptoms as adults. But a form of anxiety state peculiar to the adolescents is the condition known as school phobia or separation anxiety. This is illustrated by Case 8.

Case 8—A girl, aged 14, had refused to attend school for a year.

Her mother was affectionate and tolerant. Her father died during her infancy. Her three sisters and brother, all older than her, were well-adjusted. Her non-identical twin had a congenital heart lesion.

Her mother remarried when she was six and she remained with her mother and step-father. Although they did not quarrel openly in front of the children, they had separated on three occasions, the most recent being three weeks before her admission. She was a quiet, shy child, attached to her home, and her mother often confided her troubles in her.

She had refused to go to school since her mother had had a cholecystectomy a year previously and would scream and struggle if attempts were made to take her. Her school phobia was an expression of anxiety associated with the long-standing marital disharmony and was precipitated by her mother's operation which threatened her only stable attachment. Her phobia had prevented her mother from going out to work and allowed the patient to be near her all the time.

Table XIX shows the duration of follow-up and prognosis in this group of 25 male and 8 female patients. Five were worse on follow-up. Four males and one female had developed schizophrenia and they were all in hospital. Therefore, in this small series, 15 per cent. of patients presenting with an anxiety state became schizophrenic.

TABLE XIX

Follow-up in Years	Sex		Recovered	Improved	No Change	Worse	Total
Two	Male ..	..	1	1	0	0	5
	Female ..	..	3	0	0	0	
Three	Male ..	..	4	3	0	2	12
	Female ..	..	1	1	0	1	
Four	Male ..	..	4	0	0	1	5
Five	Male ..	..	3	3	2	1	11
	Female ..	..	2	0	0	0	
Total	..	..	18 (55%)	8 (24%)	2 (6%)	5 (15%)	33

Although there was a family history of mental illness in thirteen patients, none of these became schizophrenic. Therefore a negative family history tended to be associated with a bad prognosis, perhaps because there were less reactive factors in this group.

Table XX shows that a stable background favoured a good prognosis.

TABLE XX

Background		Recovered	Improved	No Change	Worse	Total
Stable ..	..	15	2	1	3	21
Unstable ..	..	3	6	1	2	12

There was no relationship between sex, duration of hospital stay or intelligence and prognosis. But the outlook was better in this small series when the EEG record was stable.

TABLE XXI

EEG		Recovered	Improved	No Change	Worse	Total
Stable ..	..	7	2	1	1	11
Non-specific unstable ..	..	3	2	1	1	7

HYSTERIA

There were 14 male and 16 female patients with hysterical symptoms, severe enough to warrant hospital treatment. Presentation did not differ from adults. In Table XXII, it will be seen that three patients were worse. One male was in a Borstal institution for persistent psychopathic behaviour. Two females were in hospital with schizophrenia, forming 7 per cent. of the series.

TABLE XXII

Follow-up in Years	Sex		Recovered	Improved	No Change	Worse	Total
Two	Male ..	..	3	0	0	0	4
	Female ..	..	0	1	0	0	
Three	Male ..	..	2	3	0	0	10
	Female ..	..	2	2	0	1	
Four	Male ..	..	0	1	0	1	7
	Female ..	..	2	2	0	1	
Five	Male ..	..	1	2	1	0	9
	Female ..	..	2	2	1	0	

There was no relation between family history, duration of hospital stay or sex and prognosis. The home background also failed to influence outcome. The prognosis was better in the more intelligent patient.

TABLE XXIII

I.Q.		Recovered	Improved	No Change	Worse	Total
Below 80	..	0	2	0	1	3
80-100	..	4	6	1	1	12
100-120	..	4	3	1	1	9

There were also more recoveries amongst patients with a stable EEG.

TABLE XXIV

EEG		Recovered	Improved	No Change	Worse	Total
Stable	..	5	4	0	1	10
Non-specific unstable ..	..	2	5	2	1	10
Epileptic	..	0	1	0	0	1

AFFECTIVE DISORDER

The clinical presentation was similar to that in adults. There were fifteen patients in this group, forming only 4 per cent. of a total of 362 admissions. Thirteen were male. The rarity of adolescent affective illness contrasts with its frequency in the involutional period. The male preponderance also contrasts with middle age, where these disorders are commoner in females. Table XXV shows that over half the patients were suffering from depression, reactive to severe stress. This leaves only six patients with an affective psychosis.

TABLE XXV

Diagnosis		Recovered	Improved	No Change	Total
Reactive depression	..	8	1	0	9
Mania	..	2	1	0	3
Manic-depressive	..	1	0	1	2
Depressive psychosis	..	1	0	0	1

There were no patients in the category "worse" at follow-up.

Nine patients had a reactive depression and the two female patients came into this group. There was a positive family history in four and they all recovered. The improved patient came from a large, unstable family of eleven.

Three patients were suffering from mania. Two had a positive family history, the improved patient having an alcoholic parent. Two patients had a

manic-depressive illness; one with a negative family history and stable home recovered, the other with an unstable home and psychopathic father was still in hospital. The only patient with a depressive psychosis had a severe physical disability, pseudo-hypertrophic muscular dystrophy, but made a good recovery from the depression and remained mentally well until his death four years later. This group of illnesses was therefore characterized by a good prognosis.

The EEG was stable in four patients and showed a non-specific abnormality in ten. The prognosis was not related to those findings.

OBSESSIONAL STATE

An obsessional state is the rarest psychiatric illness in adolescence but may start at an early age, as shown by the following case history.

Case 9—A girl, aged 14, complained of repetitive habits for five years.

Her father had a peptic ulcer. Her mother was methodical and tidy. Her home background was stable and the only cause of discord between her parents was the patient's illness. Her obsessional symptoms started at the age of nine and consisted of compulsions to touch things and slowness in dressing. These symptoms were worse at home than at school. They gradually increased in severity and she ended up by following her mother everywhere and imitating anything she did or said. She was frightened her mother might die of cancer and believed her imitations would prevent this happening. However, these symptoms did not prevent her from getting to school on time.

She lost her symptoms soon after admission and group therapy revealed considerable aggression beneath her placid exterior.

The prognosis of this disorder was good, half being recovered and half improved at follow-up. There were six male and two female patients. Prognosis was not related to sex. The outcome was improved by a negative family history, three of the four recoveries coming from this group. Seven of the eight patients had a stable home. The one patient from an unstable home was assessed as improved at follow-up. The duration of hospital stay was the same in the recovered and improved groups, averaging seven months.

DISCHARGE AND FOLLOW-UP RESULTS

Table XXVI summarizes the results found by Sands on discharge and compares them with the findings at follow-up after two to five years.

TABLE XXVI

Diagnosis	Recovered	Improved	No Change or Worse	Total
Behaviour disorder:				
(a) Discharge ..	.. 1 (1%)	40 (58%)	28 (41%)	69
(b) Follow-up ..	.. 76 (38%)	43 (22%)	79 (40%)	198
Schizophrenia:				
(a) Discharge ..	.. 12 (26%)	23 (50%)	11 (24%)	46
(b) Follow-up ..	.. 15 (19%)	18 (23%)	45 (58%)	78
Neuroses:				
(a) Discharge ..	.. 10 (21%)	33 (70%)	4 (9%)	47
(b) Follow-up ..	.. 34 (48%)	25 (35%)	12 (17%)	71
Affective disorder:				
(a) Discharge ..	.. 6 (43%)	7 (50%)	1 (7%)	14
(b) Follow-up ..	.. 12 (80%)	2 (13%)	1 (7%)	15

It will be seen that the results at follow-up were better than at discharge in behaviour disorders, neuroses and affective disorders. This was most marked in the first group, suggesting that stability commonly returns with maturation of

the adolescent patient. Neurotics improved at discharge recovered twice as often as they deteriorated, and affective disorders progressed to remission. In contrast, the outcome in schizophrenia was worse at follow-up, confirming the seriousness of this condition and its poor response to psychotherapy, deep insulin and leucotomy. Further follow-up studies will be required to determine whether the phenothiazine derivatives produce better results than these earlier treatments.

SUMMARY

This paper reviews 362 patients admitted to the adolescent unit at St. Ebba's Hospital between 1949 and 1954 and followed up for over two years.

Behaviour disorders accounted for half the admissions. The prognosis was good in comparison with the adult psychopath, 38 per cent. making a complete remission. The most valuable guide to prognosis was the symptomatology. Stealing as an isolated symptom had an excellent outcome whilst a combination of stealing, violence and truancy in the same individual was of poor import. Heredity and background showed little relationship to prognosis.

A quarter of admissions suffered from schizophrenia with symptoms similar to those in adult life. The prognosis was poorer than in adults, only a fifth recovering compared with a third of adults. Heredity and background had little influence on outcome. The most significant prognostic factor was sex, twice as many females making a complete remission. Results were similar with deep insulin and psychotherapy.

A quarter of patients suffered from neuroses and affective disorders. Obsessional states and affective psychoses were rare, each forming 2 per cent. of admissions, and their prognosis was excellent.

Schizophrenia developed in a few patients originally placed in other diagnostic categories. This was most common with anxiety states (15 per cent.), less with hysteria (7 per cent.) and rare in behaviour disorders (1 per cent.). No patients with obsessional states or affective disorders developed schizophrenia at follow-up.

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I am indebted to Miss Simpson for the recent follow-ups.

THE PSYCHOLOGICAL DISTURBANCES ASSOCIATED WITH 345 PREGNANCIES IN 137 WOMEN

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THE late Dr. Vera Norris (5), in a study of London mental hospital admissions, found that a London woman, at birth, has 0·8 chances in 1,000 of being admitted at some time in her life with a puerperal psychosis. This figure, based upon hospital admissions, must be compared with Kline's (4) estimate that 5 per cent. of pregnant women have an associated emotional disturbance. Clearly, hospital admissions represent a small proportion of all cases occurring and it is likely that socio-economic and cultural as well as medical factors play a part in determining whether admission takes place. Estimates of the incidence of psychiatric disorders associated with childbearing must vary according to the age structure of the population, the facilities for psychiatric care available in the community and the criteria adopted for attributing illness to the effects of childbearing.

Opinion is divided concerning the nature of mental breakdowns associated with childbearing, but the majority of recent authors consider that the disorders occurring in association with childbearing are indistinguishable from those occurring at other times (Fondeur, *et al.* (2); Vislie (9); Jacobs (3)). Seager (8) has recently reviewed the literature and given an account of a series of puerperal women admitted to a mental hospital who were compared with non-puerperal admissions and with psychiatrically normal puerperal women. He concluded that there was no evidence for a specific puerperal mental disorder, but that the puerperium acted as a stress, precipitating breakdown in the predisposed woman.

It seems reasonable to suppose that pregnancy and childbirth could have an effect upon mental function both in a psychodynamic and in a physiological way. The evidence for a physiological effect is strongest for those disorders occurring (and recurring) at the time of the most dramatic physiological change, namely, delivery.

The present paper reports a study carried out in general practice upon a series of women delivered in recent years. The aim of the study was both to assess the incidence of psychiatric disorders associated with childbearing, including mild disturbances, and to indicate, if possible, the nature of the effect of childbearing upon mental health. Neither psychiatrists nor obstetricians have access over prolonged periods to unselected populations in the way that G.P.s have; in my own case the normal G.P.'s knowledge of his patients' backgrounds and temperaments has been supplemented by a previous study which has established the rates of psychiatric disturbances in the practice population (Ryle (7)). It is therefore possible to compare the rates of psychological disturbances in women at the time of childbearing with the rates in women of similar age in the same population. In both groups a large proportion of the disorders recorded are relatively mild and hence of a type not usually encountered in hospital practice.

METHOD

The investigation has been carried out in general practice and is based upon an analysis of the records of all women who have been confined at least once between January, 1955 and October, 1959 and who are still registered with my practice. These patients have, of course, been under observation throughout the period and not only during and after pregnancy. Records were traced by two methods: in the first place, the names of 80 women whom I had personally cared for during pregnancy and labour were obtained from my obstetric records. This group included 7 patients registered on the list of one of my partners; these patients were included in the survey. No complete register of hospital confinements was available, so the remaining patients were traced from the list of new registrations of babies on the list. A special form (E.C.58) is used for this purpose. Some cases will have been missed, as parents may lose this form and use another one (E.C.1). Such cases of omission as have come to light have not been included, as they might represent a selected group noticed on account of symptoms. An examination of the records selected in this way showed that over 90 per cent. of all confinements had taken place while the woman was registered with the practice; it was therefore decided to include all pregnancies in the study, even when they had occurred before 1955.

One E.C.58 registration traced in this way was no longer on the list because her mother had committed suicide while suffering from puerperal depression. This case was included in the series. This method of selection excluded patients who had had abortions but no full term pregnancies during the period under review. The basic information recorded for these women included the following: (1) Age at last confinement. (2) Parity at the time of the study. (3) History of psychological disturbance starting (a) in pregnancy, (b) in first three post-partum months, (c) in the 3rd to 12th post-partum months, (d) at any other time. (4) Where a psychological disorder had occurred, a record was made if it had at any time necessitated three or more consultations in the course of one year, as this criterion had been used as a level of minimum severity for inclusion in the practice prevalence survey. (5) The diagnosis was recorded. Three diagnostic groups were employed, namely: (a) reactive disorders, (b) depression with endogenous features, (c) uncertain. There were no schizophrenic breakdowns. The criteria for distinguishing neurotic from endogenous depression are still a subject for debate and this distinction presents particular difficulty in mild cases.

In the present study where an attempt was being made to assess the relative importance of psychological and physiological features two commonly used criteria for the diagnosis of endogenous depression, namely the association with childbearing and the absence of psychological provocation were clearly not applicable. The presence of endogenous factors was recorded, therefore, when the following features were observed: sleep disturbance characterized by early waking, diurnal mood swing, frigidity in the absence of conflict with the husband, loss of concentration and interest, loss of feeling, lack of response to environmental change, retardation and self-accusation. Brief case histories illustrating the application of these criteria are given below. (6) The patients with reactive disorders were also classified into categories according to the apparent relationships of the pregnancy to the psychological disturbance. These categories were: (a) pregnancy and childbirth irrelevant to the disturbance; (b) pregnancy or childbirth as a socio-economic burden; (c) pregnancy or childbirth as an aspect of an emotional problem; (d) uncertain.

It should be recorded, in passing, that this practice is situated in an

industrial London borough and is composed largely of skilled workers and their families, living in tenements, converted houses or Council flats. Eighty-eight per cent. of a random sample of households belonged to Social Class III of the Registrar General's classification.

RESULTS

Records of 137 women delivered of at least one full-term pregnancy during the period of the investigation were traced; by January, 1960 these women had had, in all, 313 full-term pregnancies and 32 miscarriages. This latter figure may be incomplete. Seventy-eight of this group of women had no record of any psychiatric disturbance, 33 had a record of disturbance in pregnancy or during the post-partum year and 26 had a record of disturbance at other times. The parity and age distribution of these three groups are recorded in Tables I and II. The marital history of the whole group, in so far as it is

TABLE I

Parity of 137 Women in 1960 Classified According to Psychiatric History

	Num- ber	Parity					Aver- age Parity	Mis- car- riages
		1	2	3	4	5+		
No psychiatric history ..	78	17	39	16	6	0	2.1	16
Psychiatric disturbance in preg- nancy or the post-partum year	33	9	9	8	4	3 (5 each)	2.5	5
Psychiatric disturbance not in pregnancy or post-partum year	26	7	11	4	3	1 (10)	2.4	11
Whole group	137	33	59	28	13	4	2.3	32

TABLE II

Age at Last Confinement of 137 Women Classified According to Psychiatric History

	Number	Age at Last Confinement				
		Under 20	20-24	25-29	30-39	40
No psychiatric history	78	3	17	25	32	1
Psychiatric disturbance in pregnancy or post-partum year	33	2	11	6	14	0
Psychiatric disturbance not in preg- nancy or post-partum year ..	26	3	7	7	8	1
Whole group	137	8	35	38	54	2

known to me, is relatively eventful. Five of the women are in their second marriage. Three others are separated or divorced, 3 have stable but non-legal unions and 1 is unmarried, living with her family. Fourteen of the remainder have consulted at some time with symptoms relating to marital stress. Twenty-two of the 33 patients who had some psychological disturbance during pregnancy and the post-partum year were classified as reactive disorders and in the majority of this group (17 cases) the illness represented a reaction to a situation or relationship connected with the pregnancy. In 6 of these cases the problems were socio-economic; in the remainder they were emotional and in nearly every case associated with a disturbed marriage relationship. Seven patients presented with depression with endogenous features. In 4 patients there was inadequate information for classification.

In order to demonstrate the effect of childbearing upon mental health the rate of disturbance associated with it must be compared to the rate amongst

women in the same population who have not borne children. For this purpose the one-year prevalence rates for women aged 20-39 for the practice population as a whole can be used, although naturally these rates include women who have borne children. These rates have been calculated for two separate periods (July, 1957 to July, 1958 and January-December, 1960) (Ryle (7)). The rates for these two periods were very similar; those for the latter period are as follows: annual female prevalence rate (aged 20-39) for reactive disorders, 95 per 1,000; endogenous depression, 5 per 1,000; total rate 100 per 1,000. In the calculation of these rates cases were only included where there had been 3 or more consultations in the course of one year. By adopting this same criterion for the women in this present study, a rate of illness can be calculated (as episodes per patient-year) either for the year from conception or for the post-partum year. The total number of episodes of illness meeting this criterion occurring in the pregnancy or the post-partum year is 27, of which 23 were associated with the 313 full-term pregnancies and 4 were associated with the 32 miscarriages. The time of presentation of these disorders, classified by diagnosis, is presented in Table III. It is seen that 15 episodes of illness occurred

TABLE III

Episodes of Psychiatric Disorders Related to 313 Full-term Pregnancies and 32 Miscarriages, Classified According to Time of Presentation and Diagnosis, Excluding Cases in Whom there were Fewer than 3 Consultations

Time of Presentation	Reactive Disorders	Endogenous Depression	Uncertain	Total
During pregnancy	7	0	1	8
0-3 months after delivery	3	6	1	10
3-12 months after delivery	3	2	0	5
During pregnancy ending in a miscarriage	3	0	0	3
After miscarriage	0	1	0	1
Total	16	9	2	27

in 313 post-partum years (excluding abortions), a figure which corresponds to a one-year prevalence rate of 48 per thousand. The equivalent one-year prevalence rate for 1959 for women aged 20 to 39 on my list was double this figure. If reactive disorders and cases with symptoms of endogenous depression are separated it is apparent that the rate for reactive disorders is markedly lower in the post-partum year (19 per thousand as against 95 per thousand) whereas the rate for depression with endogenous features is markedly higher (26 per thousand as against 5 per thousand). In the 1959 prevalence survey only two women aged 20-39 presented evidence of endogenous depression out of 423 at risk and one of these was, in fact, during the post-partum year (Case 26 of the present paper). Further support for the view that childbirth precipitates endogenous depression is obtained from a study of the time of development of symptoms. The post-partum three months represents one-seventh of the period associated with pregnancy studied in the present investigation. Three out of 13 episodes of reactive disorder first presented during this period but, of the 8 episodes of endogenous depression, no fewer than 6 occurred within three months of delivery.

CASE HISTORIES

Selected case histories of patients who consulted 3 or more times in the year are given to illustrate the principles upon which the classification has

been based. All patients considered to show evidence of endogenous depression are reported. No examples are given from the group in which the pregnancy appeared irrelevant to the disturbance.

(a) *Reactive Disorder: Pregnancy as a Socio-economic Problem*

Case 6

By the age of 25 this patient had five children. They lived in a dark, damp basement. She had occasional mild depressive spells and when her youngest child was 2 she had a more pronounced depression with sleep disturbance and some episodes of depersonalization. At this stage she became pregnant after a contraceptive failure; she became increasingly depressed and made a not very determined suicidal attempt by gas. Termination of the pregnancy and sterilization was carried out on psychiatric advice. This patient was diagnosed as a neurotic depression in an hysterical personality. Her symptoms did not return after operation.

Case 9

A girl of 18 whose husband was called up ten weeks after her delivery, leaving her alone in her mother-in-law's house, became depressed. A few weeks later she was discovered to be pregnant again, became very depressed and lost much weight. She recovered when her husband obtained a home posting.

(b) *Reactive Disorder: Pregnancy as an Aspect of an Emotional Problem*

Case 12

This patient had her first child at the age of 30; pregnancy was complicated by an A.P.H., repeated painful attempts at induction and a long labour. She was married to a man of rigid religious views who provided very little emotional support. She became unintentionally pregnant two years after her first delivery and reacted to the pregnancy with much depression and rejection, both because of her husband's attitudes and because of her fear of a repetition of the complications of her first pregnancy. She threatened suicide, but a psychiatrist who was consulted did not feel that there was a real danger of this. She was treated with reassurance and support and an undertaking on my part to carry out the confinement which was, in fact, uneventful. She has continued to have phases of mild anxiety and depression since from time to time. This case was regarded as a neurotic depression, precipitated by pregnancy, occurring in the context of an unsatisfactory marriage.

Case 19

This patient, after a long series of miscarriages, conceived at the age of 34 for the ninth time and on this occasion the pregnancy was successful. Ten weeks after her confinement, the husband announced his intention of leaving her for a woman with whom he had been unfaithful; the patient thereupon took an overdose of barbiturates and was admitted to hospital in coma. She was successfully resuscitated. The marital situation remained unsatisfactory for a further two years, but there were no further suicidal attempts. This patient was regarded as having a severe neurotic depression occurring as the result of her husband's threatened defection soon after the successful conclusion of a long awaited pregnancy.

Case 20

This patient was married at the age of 17 and had three children in the course of the next four years. The third pregnancy was unintentional and was strongly rejected initially. During the year following the third confinement she complained of depression, fatigue, feelings of unreality and depersonalization. She tended to ruminate over dreadful things and became frigid. Her personality was obsessional and she had some compulsive rituals. She then conceived for the fourth time and became severely depressed; for the first time she expressed hostility towards her husband; she felt she had married too young and that she was tied down to the house while her husband gambled and was seldom in. She was referred for psychiatric opinion and termination was advised and carried out. She developed a post-operative pyrexia and was nursed in isolation and developed a brief agitated depression at this stage, but has remained reasonably well during the six months since. This case was diagnosed as a neurotic depression exacerbated by an unwanted pregnancy in a woman of predisposed personality whose marriage was unsatisfactory.

(c) *Depression with Endogenous Features Associated with Childbirth*

Case 24

This patient was the only child of a broken marriage; during adolescence she had some neurotic disturbance connected with her relationship with her mother. She married at the age of 23 and has had three full-term pregnancies and a miscarriage since. Her relationship with her

husband and children is good. A month after the birth of her second child, when she was 27, she developed an acute fear that she had Hodgkin's disease, and over the following six months she had a series of similar acute panics. She felt humiliated by her fears, was generally low spirited, could not concentrate and felt "heavy" in the morning, although she usually slept well. Her mother had been staying in the house since the birth of the child and the patient felt (but did not express) a good deal of resentment at the mother's tendency to take over the running of the household and children. The condition improved gradually after the mother's departure, but it was more than a year before she felt really well. Three years later she had a third child, delivery being complicated by a profuse P.P.H. There was no depression after this birth but a year later a further pregnancy ended in a miscarriage with very heavy loss necessitating transfusion, and shortly after this she became depressed again and expressed the fear that she was developing the same type of illness as she had had after her second confinement. She became frigid and could not sleep for more than three or four hours. Her mother had run the house on her return from hospital and reiterated how she had previously advised against further pregnancies. The depression gradually lifted over the ensuing months.

Case 25

At the age of 18 this patient developed insomnia, a fear of madness and anxiety, following the V.2 rocket attacks on London. She saw a psychiatrist, who thought she had a schizoid personality. She recovered after a few months' psychotherapy. Her father had had similar illnesses after the 1914-18 war and in 1941. She had a first child at the age of 26 and was rather depressed after the confinement but did not see a doctor for this. She was delivered of her second child when she was 31. Four days after delivery she became tearful and she became increasingly depressed in ensuing weeks. She had recently moved to the suburbs but had returned to her parents' house for her confinement. On returning to her own home her depression became worse; she could not go out for any distance alone, especially not past the local mental hospital. Rather than go to the psychiatrist there she returned to her parents' home where her depression improved after nocturnal sedation and methyl amphetamine by day and some supportive psychotherapy. She complained for some time of disturbed sleep (early waking) and she said she had not got any real feeling for the baby. Her depression improved steadily, but she developed panic attacks while out shopping and, after some time returns to her new house, abandoned the idea of living there and moved back into the parental home. In the two years since she has had minor anxiety symptoms only; she works as a catering manageress part-time and enjoys her children.

Case 26

This patient conceived before marriage at the age of 19. Ten months after delivery she complained of headaches, premenstrual depression and lack of energy; she wept easily. Three years later she had a second child and six months after delivery she presented with headaches, depression (worse in the morning), forgetfulness and a decrease in her sexual feelings.

Case 27

This patient had some psychotherapy at the age of 16, at which time she was under stress as a result of her parents' objection to her association with an older married man. Eventually her parents accepted the association and the couple have lived since in the parents' home. At the age of 24 she became pregnant; the pregnancy was welcomed but she became rather anxious and, as a result of a fear of hospitals, booked for a home confinement. In fact she had to go into hospital for induction, but labour was otherwise uneventful. Two weeks later she became irritable, tearful, forgetful and fatigable; she began to have difficulty in getting off to sleep and woke early and was noticeably more depressed in the mornings. She did not feel as warmly towards the child as she had expected to. In the ensuing weeks she was treated with methyl amphetamine by day with nocturnal sedation and supportive psychotherapy. She remained very irritable, especially towards her mother who tended to try to take over the baby's management. She was frigid for six months after her confinement.

Case 28

This patient first became pregnant at the age of 19. She had an ante-natal admission for A.P.H., a premature labour and a P.P.H. Four weeks after her confinement she became very depressed and was referred to a psychiatrist, who gave intensive supportive therapy and sedation. She was much improved after four weeks. Her second pregnancy resulted in the birth of twins, one of whom died soon after birth and the other of whom died some months later without having ever left the hospital. She became severely depressed soon after her delivery and while under out-patient treatment she attempted suicide and was admitted to a mental hospital. Her condition at that time was described as "retarded and bewildered". She expressed a delusional idea about being incredibly filthy and deserving to be in prison. She recovered after E.C.T. Sterilization was recommended but not carried out, and this was perhaps fortunate, for she has had two further pregnancies, including the successful delivery of twins, without further breakdown.

Case 29

This patient committed suicide in 1956 and records are not available. She was aged about 30, married, against family opposition, to an Indian clerical worker. She had had a stillbirth one year before the delivery of her child. She had no untoward psychological reaction to this, but soon after delivery of her child she became depressed and self-accusatory and was admitted to hospital and treated by E.C.T. Soon after her discharge from hospital, about six months after delivery, she jumped under a train and was killed.

DISCUSSION

The present investigation shows that the rate of psychological disturbance in women in pregnancy or the post-partum year is lower than the equivalent overall rate for women of similar age in the practice population. This lower rate conceals a markedly higher rate for depression with endogenous features. The patients with endogenous depressions, with one exception, presented symptoms within three months of delivery.

In the majority of reactive cases the pregnancy or the new child operated as a psychodynamic factor in the provocation of the neurotic symptoms. None the less the rate for reactive disorders in the group is low compared to the general population. This could be explained as an effect of selection, women who bear children being, as a group, more stable and satisfied than their sisters. Evidence for a specific effect of childbearing is apparent, however, in that depression with endogenous features occurs after childbirth with a much higher frequency than in the population as a whole. It is noteworthy that in this group significant emotional disturbance is also present in most cases.

In this series of unselected deliveries, in which mild psychological disturbances are included for study, childbirth has apparently precipitated endogenous depression in about 3 per cent. of confinements. 4.4 per cent. of the women having been affected at some time. Roth (6) estimates that 10 per cent. of the population are liable to endogenous depression, and this figure of 4.4 per cent. in a population nearly all below the age of 40 is in reasonable accordance with this estimate. It would seem that the role of childbirth must be provocative rather than causative, for hospital admission rates for endogenous depression rise steadily with age (Brooke (1)) and my own practice prevalence figures, though based on few largely mild cases, show a similar tendency. If childbearing caused the disease to occur in those who would not otherwise be afflicted one would expect a peak incidence in the childbearing era. The fact that recurrence with each delivery is not automatic and the presence of obvious psychodynamic factors in most cases of puerperal depression with endogenous features suggests that childbirth, while increasing the liability of women to attacks of depression with endogenous features, cannot be regarded as the cause of the depressive illness.

The history of Case 28 emphasizes the dangers of recommending sterilization in these cases. It is probable that the operation of endogenous factors in depression occurring after childbirth is often unrecognized, symptoms being attributed to the normal fatigues of caring for small children. The risk of suicide, and the increasing efficiency of treatment, make it desirable that the diagnosis should not be missed.

SUMMARY

A general practice study of psychological disorders associated with childbearing is reported.

Thirty-three of 137 women who had been delivered at term at least once since 1955 had a record of psychological disturbance on at least one occasion

in pregnancy or the post-partum year. The rate for reactive disorders in the year after delivery was 19 per 1,000, about one-fifth the one-year prevalence rate for women of similar age in the practice population as a whole. The rate for depression with endogenous features during this year was 26 per 1,000, about five times the equivalent annual prevalence rate and nearly all the attacks occurred within three months of delivery. There is some evidence that delivery precipitates endogenous depression.

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A COMPARISON OF TETRABENAZINE AND CHLORPROMAZINE IN CHRONIC SCHIZOPHRENIA

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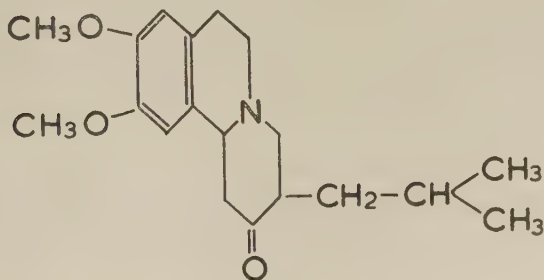
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At the present time only two groups of drugs have an established place in the treatment of chronic schizophrenia, the phenothiazine derivatives and the rauwolfia group of alkaloids. Of these two groups the phenothiazines are in more general use, and, although not free from side-effects, are safer drugs for the long-term management of schizophrenic patients. They also have a wider range of effectiveness in the different schizophrenic syndromes. Many observers, however, have been impressed by the dramatic results obtained in a proportion of cases of long-term schizophrenia treated with the rauwolfia alkaloids and these may be effective in cases not responding to the phenothiazines (Kline, 2).

Tetrabenazine is a new drug of considerable theoretical interest.



It is a benzoquinolizine derivative and its pharmacological properties have been described in detail by Quinn *et al.* (4). Its effects in producing sedation in the experimental animal are similar to those of reserpine. After a single injection of tetrabenazine there is a fall in the concentrations of 5-hydroxytryptamine

* This work was carried out when the first and third authors were registrars in the Craig House section of the Royal Edinburgh Hospital.

and catecholamines in the brain and an increased excretion of 5-hydroxy-indolyl-3-acetic acid in the urine. The sedative effect of the drug closely parallels in time the depletion of brain amines. The brain hydroxytryptamine concentration returns to normal within twenty-four hours whereas in the reserpine-treated animal it remains depressed for six to seven days. If administration of tetrabenazine is preceded by premedication with iproniazid the animal becomes excited and the brain 5-hydroxytryptamine shows only a slight decline.

Clinical trials of tetrabenazine have been carried out by Voelkel and Dresler (5) and Lingjaerde (3). These workers report improvement in chronic schizophrenic patients and did not encounter serious side-effects. An important point which has emerged from both experimental and clinical studies is that cardiovascular complications such as the bradycardia and hypotension produced by reserpine do not occur. This may be because tetrabenazine, unlike reserpine, does not reduce the concentration of noradrenaline in peripheral tissues (Quinn et al., 4).

We report here a controlled trial of tetrabenazine in the treatment of chronic schizophrenic patients. The trial was designed to obtain answers to the following questions. (a) Does the drug compare favourably with chlorpromazine, a standard treatment in this type of patient? (b) What is its range of usefulness? (c) What are the side-effects? In order to answer these questions as comprehensively as possible a wide range of chronic schizophrenic patients, classified according to principal symptoms, was chosen. Several elderly patients were included in order to assess the safety of the drug in this age group.

THE CLINICAL TRIAL

Fifty-two long-term female schizophrenic patients, duration of illness three to thirty-four years, from five wards of the hospital, were chosen for the trial.

They were divided into two groups by a colleague whose only other role in the trial was the dispensing of the drugs. The groups were matched by him for age, clinical assessment, behaviour rating on the scale of Baker and Thorpe (1) and previous leucotomy.

Each group contained 26 female patients. The mean age in the tetrabenazine group was 56.1 (standard deviation 12.8). The mean age in the chlorpromazine group was 58.3 (standard deviation 11.0). Four patients in each group had had a previous leucotomy. The mean initial behaviour rating scores were not significantly different in the two groups, being 82.3 (standard deviation 39.7) in the tetrabenazine group and 82.5 (standard deviation 38.6) in the chlorpromazine group.

Neither the authors nor the nurses knew to which group the patients had been allotted, until completion of the trial. Supplies of matching capsules were obtained containing chlorpromazine 75 mg. or tetrabenazine 30 mg. or an inert placebo. The patients were studied for twenty weeks, the trial period being divided into three stages:—

First six weeks. All day-time medication was discontinued at the start of this period except in three patients who required a sedative of sodium amytal 200 mg. t.i.d. on account of disturbed behaviour. Night sedation was standardized; when a sedative was required sodium amytal 200 mg. was prescribed. In all other respects the ward routine was continued as usual. At the beginning of the sixth week the nursing staff began to fill in daily behaviour rating charts for each patient.

Seventh and eighth weeks. During these weeks one placebo capsule was administered three times daily to all patients in the trial.

Ninth to twentieth weeks. The patients received either tetrabenazine or chlorpromazine according to the group to which they had been allocated. For the first four weeks of active treatment (weeks 9 to 12) one capsule three times daily was administered and for the last eight weeks (weeks 13 to 20) one capsule four times daily. Thus the patients received tetrabenazine 90 mg. or chlorpromazine 225 mg. daily for four weeks and then tetrabenazine 120 mg. or chlorpromazine 300 mg. for eight weeks.

ASSESSMENT

The mental state was assessed by two methods.

Clinical Examination

A detailed mental examination was carried out during the placebo period and during the twentieth week of the trial. Each patient was interviewed by the same doctor on both occasions. At the first interview the following psychotic symptoms were especially sought; disorder of affect, thought disorder, hallucinations, delusions, ideas of reference and catatonic signs. The information obtained was utilized by the colleague who divided the patients into two groups. On re-assessment at the second interview, the patients were rated as definitely improved, no change or worse. Any marked change in one symptom, e.g. thought disorder, was also noted.

Behaviour Rating

From the beginning of week 6 each patient was assessed daily by the nurse-in-charge on ten items according to the behaviour rating scales of Baker and Thorpe (1). The rating scale scores were used to measure two aspects of behaviour as described by Baker and Thorpe, viz.:

(a) *Schizophrenic Deterioration.* This was measured by the sum of the ratings of the ten scale items. The daily marks for the ten items on the scale were added together to give a weekly score for each patient.

(b) *Restlessness.* The sum of the weekly totals for two items in the scale, viz., day and night restlessness, were used as a measure of psychomotor restlessness.

Physical Examinations

These were carried out by one of the authors (E.M.) during weeks 6 and 20. Pulse rate, blood pressure and E.S.R. were recorded.

RESULTS

Six patients in the tetrabenazine group and two patients in the chlorpromazine group failed to complete the trial. Of the former, one was withdrawn because of the objection of a relative and five because of side-effects which are described below. One patient in the chlorpromazine group had a cerebral thrombosis during the seventh week of the trial, when receiving the placebo, and another absconded from the hospital during the fourth week of the trial.

BEHAVIOUR RATINGS

*Schizophrenic Deterioration*TABLE I
Mean Rating Scores

	No. of Patients Completing Trial	Week 6 No Treatment	Week 20 After 12 Weeks' Treatment	Significance of Difference
Tetrabenazine ..	20	82.4±40.1*	62.6±33.6	P=<0.01
Chlorpromazine ..	24	85.1±42.2	56.3±35.4	P=<0.001

*± standard deviation

There was a significant improvement in the mean rating scores during the trial in both groups. The trend was for the chlorpromazine group to improve more than the tetrabenazine group but the difference was not statistically significant.

TABLE II
Mean Restlessness Scores

	No. of Patients Completing Trial	Week 6	Week 20	Significance of Difference
Tetrabenazine ..	20	8.2± 9.4*	5.7±5.5	P=>0.05
Chlorpromazine ..	24	10.8±11.7	4.5±5.7	P=<0.02

*± standard deviation

There was no significant change in the mean restlessness scores of the tetrabenazine patients but there was a significant improvement in the scores of the chlorpromazine group.

It was also our clinical impression that psychomotor over-activity was better controlled in those patients who later proved to have been receiving chlorpromazine.

An analysis of the results as assessed at clinical interview can be summarized as follows. Twenty-four patients in the chlorpromazine group and twenty in the tetrabenazine group completed the trial. Six patients receiving chlorpromazine showed definite improvement, one deteriorated and seventeen showed no change. Of the tetrabenazine group, seven showed definite improvement, one deteriorated and twelve did not change.

An analysis of the improvement in the main symptoms reveals the following picture (Table III).

TABLE III
Analysis of Improvement in Individual Symptoms

	Thought Disorder	Catatonic Signs	Paranoid Symptoms	Affective Disturbance
Chlorpromazine ..	1	2	1	2
Tetrabenazine ..	4	2	1	0

These numbers are too small for valid statistical analysis, but the improvement in thought disorder in some of the patients receiving tetrabenazine was very marked; this is illustrated by the following case history:

Case 1

A married woman, aged 58, had been in hospital for fourteen years. At the start of the drug trial she was withdrawn and showed marked affective blunting, auditory hallucinations and a very gross thought disorder. Asked how she was, she replied, "Why do we have to see an engine?" and then said, "How's your toothache?" By the end of the trial it was possible to carry on a fairly normal conversation with her, and to the above question, she replied, "I'm feeling very fit, thank you. What was wrong when I was brought here?" She admitted to auditory hallucinations but subsequently (tetrabenazine having been continued) these ceased and it is now difficult to detect any abnormality in her stream of thought. She still shows affective blunting, however, and retains certain delusions, but continues to improve slowly.

Physical Effects

Table IV shows a comparison of blood pressure, pulse rate and E.S.R. before and after the trial. The blood pressures and pulse rates were recorded when the patients had been at rest in bed for thirty minutes.

TABLE IV

Mean Readings and Standard Errors of Blood Pressure, Pulse Rate and E.S.R. Before and After the Trial

		6th Week	20th Week	P=
Tetrabenazine:				
Systolic blood pressure	..	149.3±6.4*	138.3±7.3	>0.05
Diastolic blood pressure	..	88.5±3.4	78.0±3.7	<0.05
Pulse rate		77.5±0.2	77.0±5.7	>0.05
E.S.R.		17.6±8.4	22.3±8.4	>0.05
Chlorpromazine:				
Systolic blood pressure	..	152.9±5.7	135.0±5.4	<0.05
Diastolic blood pressure	..	88.9±7.9	77.5±6.0	<0.001
Pulse rate		76.9±1.4	84.0±5.9	<0.01
E.S.R.		17.9±7.1	26.7±4.1	>0.05

*±standard deviation

In the tetrabenazine group the only significant change was a fall in diastolic blood pressure, whilst in the chlorpromazine groups both diastolic and systolic blood pressure showed a fall and the pulse rate a significant increase.

SIDE-EFFECTS

These were most troublesome in the tetrabenazine group, five of these patients being withdrawn because of severe side-effects. Of the five, two developed a subacute delirium, one a generalized tremor, one marked unreality feelings and agitation, and one became suicidally depressed. The side-effects which were not severe enough to necessitate withdrawal from the trial were as follows. In the tetrabenazine group, one patient developed a recurrent catatonic stupor, one a Parkinsonian syndrome, two became extremely drowsy during the first week of therapy and four showed severe motor restlessness. In the chlorpromazine group, four patients developed Parkinsonism, four showed drowsiness in the early stages of treatment and one developed a severe fine tremor of the hands.

The side-effects in the chlorpromazine group are consistent with previous reports.

The side-effects in the tetrabenazine group call for a more detailed description.

1. *Subacute delirium.* Two patients, aged 79 and 78 (the eldest two in the trial) developed a subacute delirious state with clouding of consciousness, restlessness, particularly at night, and in one case incontinence. These symptoms came on during the first week of treatment and it was necessary to discontinue the drug, when they disappeared within twenty-four hours.

2. *Severe motor restlessness* appearing within a week of commencing the drug was apparent in four catatonic patients who had previously shown little activity.

3. *Catatonic stupor.*

Case 2

A 62-year-old patient, who had been in hospital for eleven years, showed a peculiar transition to a periodic type of catatonic syndrome when started on tetrabenazine. Before the trial she spent most of the day sitting in one position and her gross thought disorder only rarely emerged in speech. On the second day of tetrabenazine treatment she lapsed into catatonic stupor. During the next six weeks, episodes of stupor lasting two to three days alternated with periods of near normality of approximately one week's duration. During the last six weeks of the trial, however, the periodicity disappeared and her condition returned to a state little better than the pre-treatment level.

4. *An extra-pyramidal syndrome* of Parkinsonian type with tremor, rigidity and mask-like facies but without sialorrhoea was seen in one patient (Case 1).

5. *Depression.* One patient in the tetrabenazine group became depressed during the trial.

Case 3

A single woman, aged 76, with a schizophrenic illness of thirty-two years' duration, had a history of depressive symptoms in 1938 but these had not since been a feature of her illness. During the fifth week of tetrabenazine treatment she developed a typical depression with retardation and suicidal thoughts. The tetrabenazine was discontinued but she remained extremely depressed expressing the belief that her internal organs had ceased to function and that there was no hope for her. After four weeks she was given a course of seven electro-plexy treatments and the depression cleared. She reverted to her previous hallucinatory schizophrenic state.

6. *Impulsive suicidal attempt.*

Case 4

A single woman, aged 36, with a schizophrenic illness of twelve years standing appeared to be improving when she suddenly attempted suicide by throwing herself over a bannister. This act appears to have resulted from her awareness of her position in a long-stay ward with other chronic patients. She was not injured and there was no repetition of this impulsive behaviour. The tetrabenazine was discontinued, however, and she was transferred to another ward.

DISCUSSION

We can now attempt to answer the questions posed at the start of the trial.

1. The results of the trial suggest that tetrabenazine, like chlorpromazine, is of value in the treatment of chronic schizophrenia.

2. Where restlessness and over-activity are prominent features, chlorpromazine is superior to tetrabenazine, but the latter drug is of particular value in cases where thought disorder dominates the clinical picture.

3. Side-effects of tetrabenazine are more numerous than those of chlorpromazine but the former drug is free from the cardiovascular complications of reserpine therapy. All side-effects, with the exception of depression, subside within 24 hours on discontinuation of treatment.

The development of depression during administration of tetrabenazine suggests that the drug may share with reserpine the potentiality of producing a depressive state and that it should therefore be used with caution in cases of

schizophrenia showing a strong affective component. The depression in our case responded rapidly to electroplexy when it had failed to resolve spontaneously. It is of interest to record here that Lingjaerde (3) and Voelkel and Dresler (5) found that tetrabenazine causes no prolongation of the apnoeic phase after electroplexy therapy and state that the two treatments may be used concurrently.

The motor restlessness and agitation seen in some of our tetrabenazine-treated cases may be analogous to the turbulent phase sometimes seen during the early stages of reserpine therapy.

We consider that tetrabenazine has a place in the treatment of patients with long-standing schizophrenia, particularly those who have responded little (or not at all) to the phenothiazines. It seems to be of particular value in the amelioration of the symptom of thought disorder. The number in our trial is small and it must be regarded as a pilot study. We feel that further studies are required to amplify the information so far available. In particular a trial of the drug in acute schizophrenia would appear to be a logical development.

It is of particular interest to note that the possible clinical usefulness of tetrabenazine was deduced from a knowledge of its biochemical and pharmacological action in animal studies. It is to be hoped that the development and study of the actions of this and other new psychotropic drugs will lead to further advances in the elucidation of the aetiology of the psychoses.

SUMMARY

1. A controlled trial was carried out to compare the efficacy of tetrabenazine with that of chlorpromazine in chronic schizophrenia. Fifty-two female patients in two matched groups were studied over a period of twenty weeks.

2. Both groups of patients showed significant improvement during treatment. The trend was for chlorpromazine to be more active in controlling psychomotor over-activity and for tetrabenazine to be particularly effective in lessening thought disorder.

3. Although side-effects caused suspension of treatment in five patients in the tetrabenazine group, the drug may be safely administered to patients in hospital and appears to be worthy of more extensive trial.

ACKNOWLEDGMENTS

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THE USE OF GLUCAGON IN THE TERMINATION OF INSULIN COMA

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GLUCAGON, the hyperglycaemic glycogenolytic factor of the pancreas, was discovered by Kimball and Murlin in 1923 (1). It was crystallized by Staub, Sinn and Behrens in 1953 (2, 3). Glucagon is believed to cause a rise in blood sugar by acting at the site of liver phosphorylase—converting inactive phosphorylase to active phosphorylase (4).

As the authors still believe that deep insulin coma therapy is a valuable therapeutic procedure in those early cases of schizophrenia that are resistant to the phenothiazines, it was proposed to study the effects of glucagon on patients in insulin induced coma, and to assess the efficacy of glucagon as a means of interruption.

MATERIALS AND METHODS

The patients included in this study were all inpatients at Deva Hospital. They had been diagnosed as suffering from schizophrenia, and were undergoing deep insulin coma treatment. They were all males and were all in good physical health. The routine of insulin treatment was not altered in any way. Insulin was given at approximately 7 a.m., usually the patient entered coma some three hours later. For the purpose of this study, blood specimens were withdrawn from the antecubital vein. Six specimens were taken.

1. Before administration of insulin, i.e. fasting blood sugar.
2. At sopor.
3. At coma.
4. Just before the administration of glucagon.
5. Five minutes after the administration of glucagon.
6. Ten minutes after the administration of glucagon.

Patients were considered to be in sopor when:

- (a) Lightly unconscious. Could not be roused, and were unable to respond to auditory stimuli.
- (b) Made purposive responses to painful stimuli.
- (c) Presence of superficial and deep reflexes.

(d) Babinski's sign was absent.

Patients were considered to be in coma when:

- (a) Deeply unconscious.
- (b) No responses to painful stimuli.
- (c) Absence of superficial and deep reflexes.
- (d) Babinski's sign was present.

They were allowed to remain in coma for 20 minutes and were then given glucagon 2 mg. (in solvent) intramuscularly into the side of the thigh. The dosage was arrived at following preliminary studies done in 1959. It was found that amounts greater than 2 mg. were no more effective than that

RESULTS

Date		Fasting Blood Sugar	Sopor	Coma	Glucagon	Blood Sugar at 5-minute Intervals After Glucagon		Apur- posive Re- sponses	Pur- posive Re- sponses	Ques- tions An- swered Correctly
Patient: P.L. Age 23 years. 665 units										
13.4.60										
Time A.M.	..	7.00	9.20	10.00	10.20	10.25	10.30	10.28	10.30	10.34
Blood sugar mg. % . .	..	120	13	4	5	17	26			
14.4.60										
Time A.M.	..	7.00	9.45	10.20	10.40	10.45	10.50	10.43	10.46	10.52
Blood sugar mg. % . .	..	122	30	40	26	36	43			
20.4.60										
Time A.M.	..	7.04	9.55	10.35	10.55	11.00	11.05	10.57	11.07	11.10
Blood sugar mg. % . .	..	132	32	28	24	40	64			
21.4.60										
Time A.M.	..	7.00	9.45	11.10	11.30	11.35	11.40	11.34	11.40	11.43
Blood sugar mg. % . .	..	188	64	52	72	100	88			
26.4.60										
Time A.M.	..	7.00	9.55	10.20	10.40	10.45	10.50	10.44	10.47	10.51
Blood sugar mg. % . .	..	84	14	4	18	18	26			
29.4.60										
Time A.M.	..	7.00	9.40	10.20	10.40	10.45	10.50	10.43	10.48	10.51
Blood sugar mg. % . .	..	137	14	18	21	18	28			
3.5.60										
Time A.M.	..	7.00	9.40	10.05	10.25	10.30	10.35	10.27	10.29	10.37
Blood sugar mg. % . .	..	132	29	29	23	12	Sp. Clott.			
4.5.60										
Time A.M.	..	7.00	9.43	10.19	10.40	10.45	10.50	10.42	10.43	10.52
Blood sugar mg. % . .	..	104	12	8	7	9	20			
Patient J.S. Age 24 years. 171 units										
20.4.60										
Time A.M.	..	7.05	9.40	10.30	10.50	10.55	11.00	10.56	11.09	11.15
Blood sugar mg. % . .	..	128	40	32	34	42	44			
26.4.60										
Time A.M.	..	7.05	9.35	10.15	10.35	10.40	10.45	10.46	10.52	11.00
Blood sugar mg. % . .	..	84	19	18	28	20	20			
29.4.60										
Time A.M.	..	7.05	9.40	10.32	10.52	10.57	11.02	10.54	11.01	11.13
Blood sugar mg. % . .	..	88	18	18	11	11	18			
3.5.60										
Time A.M.	..	7.05	9.30	10.26	10.46	10.51	10.56	10.47	10.52	11.08
Blood sugar mg. % . .	..	66	31	9	21	28	31			
Patient: S.H. Age 16 years. Units 456										
13.4.60										
Time A.M.	..	7.00	9.25	10.14	10.34	10.39	10.44	10.42	10.48	10.51
Blood sugar mg. % . .	..	103	5	9	10	25	43			
3.5.60										
Time A.M.	..	7.00	9.44	10.20	10.40	10.45	10.50	10.42	10.47	10.54
Blood sugar mg. % . .	..	122	8	30	23	30	54			
29.4.60										
Time A.M.	..	7.00	9.45	10.08	10.28	10.33	10.38	10.30	10.38	10.42
Blood sugar mg. % . .	..	86	Clotted	14	18	21	28			

(2 mg. in 2 c.c. solvent) employed in the present study. After the administration the clinical condition was observed, and the return of consciousness was noted under the following headings:

- (a) Apurposive responses to painful stimuli.
- (b) Purposeful responses to painful stimuli.
- (c) Questions answered correctly, i.e. fully orientated.

As soon as full orientation was reached, the patient was then given Complan (2 ozs. to a pint of water) orally.

The results have been set out in table form as this was considered to be the clearest, least complicated, and most suitable form of presentation. On the 15 occasions when glucagon was given to patients in coma, there was a return to consciousness without recourse to any other method of interruption being necessary. The average recovery time was 15.8 minutes ranging from 11 to 25 minutes. Recovery took place in all cases without untoward incident, or relapse into hypoglycaemia.

Nasal interruption is time-consuming, rather distasteful and sometimes difficult to carry out. Aspiration of vomited material is a danger. Rhinitis is a common complication.

DISCUSSION

The desirability of a simple method of interruption in insulin coma is obvious. Intravenous interruption has disadvantages and risks, viz.:

- (a) Difficulty of finding suitable veins in obese subjects.
- (b) Phlebitis with subsequent narrowing of the lumen.

Glucagon has apparently no side-effects. Since it can be administered intramuscularly in a small volume with no local reaction, this method of interruption would appear to have many advantages. "After-shocks" could be simply dealt with by this method. It can be used also, as an emergency or diagnostic procedure in suspected hypoglycaemia, when its advantages are obvious.

After the administration of glucagon, the return to consciousness does not appear to run *pari passu* with the rise in the venous blood sugar. This might be accounted for by the rapid removal of the glucose made available, and this would merit further research. The fact that the patient's own glucose is being utilized may be considered to be an additional feature of its usefulness.

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A COMPARISON OF RESULTS IN SCHIZOPHRENICS TREATED WITH (1) INSULIN, (2) TRIFLUOPERAZINE ("STELAZINE")

By

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THERE appears to be a feeling at the moment among many psychiatrists that the treatment of early schizophrenia of all types with the recently introduced phenothiazine derivatives is as effective, if not better than, Insulin Coma Treatment (I.C.T.) and that there are many other advantages besides. In some hospitals insulin coma treatment has been discontinued altogether.

It was felt that this needed further investigation.

The phenothiazine chosen was trifluoperazine dihydrochloride (Stelazine) which had been found to be successful in chronic schizophrenia (Madgwick *et al.*, 1958).

METHOD

It was originally decided to carry out a parallel trial allotting alternate cases at random to one treatment or the other, but this was unfortunately not practicable at the time. It was decided to take the relevant information from the case notes of those patients who had had I.C.T. during the past eight years and to treat all recent schizophrenics with trifluoperazine. Only those cases who had a history of onset less than two years before the beginning of treatment were included. All patients in this survey were females.

For statistical analysis there were not enough patients for the results to be divided into more than two response categories—improved and not improved. The re-admission rate and the duration of stay in hospital have also been analysed statistically.

RESULTS

Table I shows the age distribution of the two groups of patients.

TABLE I

Treatment	Age Group				Totals
	11-20	21-30	31-40	41-50	
Trifluoperazine	1	18	15	13	47
Insulin	2	26	32	3	63

The mean age of the trifluoperazine-treated group is 35.0 years and that of the insulin-treated group is 31.8 years. There is no significant difference statistically between these two means.

Table II shows the number of patients improved or not improved in each group.

				TABLE II		
				Not Improved	Improved	% Improved
Trifluoperazine	..	..	..	3	43	94
Insulin	..	..	..	16	47	75
$\chi^2 = 5.535$				$0.05 > P > 0.02$		

The difference between the numbers improved in the two groups is significant at the 5 per cent. level.

Of those improved in Table II, 68 per cent. of the I.C.T. cases were markedly improved, while 85 per cent. of the trifluoperazine cases were markedly improved.

Table III shows the proportion of patients re-admitted at nine months from the date of their discharge: this figure was taken as being the longest period of time we could reasonably use owing to the recent introduction of trifluoperazine.

				TABLE III		
				Re-admitted	Not Re-admitted	% Re-admitted
Trifluoperazine	..	..	..	8	21	28
Insulin	..	..	..	26	18	59
$\chi^2 = 5.764$				$0.02 > P > 0.01$		

The difference is highly significant.

It was found that of those patients on trifluoperazine who had been re-admitted at nine months after discharge 27 per cent. were hebephrenics and 22 per cent. paranoid schizophrenics.

Table IV shows the duration of stay in hospital in weeks. The standard error of each mean is given in brackets.

				TABLE IV		
				All Patients	Hebe- phrenics	Paranoids
Trifluoperazine	..	..	..	11.7 (1.13)	11.6 (1.58)	11.9 (1.70)
Insulin	..	..	..	29.7 (4.42)	30.2 (6.07)	29.7 (8.67)

When all patients are considered, the difference between the mean stay in hospital for trifluoperazine-treated and I.C.T. patients is significant at the 1 per cent. level. In hebephrenics the difference is significant at the 5 per cent. level, but in paranoids the difference does not quite reach the 5 per cent. level of significance.

In view of the fact that there is almost no overlap between the period during which the I.C.T. group were admitted to hospital and the period during which the trifluoperazine-treated patients were admitted (only three of the insulin-treated patients were admitted after 1957, while all the trifluoperazine-treated group were admitted in 1958 and 1959 except for one who was admitted in December, 1957), the validity of a comparison of the length of stay in

hospital between the two groups depends on the assumption that there has been no significant trend in the duration of stay in hospital of schizophrenics during the period 1951–1959. No such trend is to be seen in the figures and an analysis of variance reveals no difference in the mean duration of stay in hospital from year to year in either the trifluoperazine-treated group or the insulin-treated group. It therefore seems safe to conclude that the marked reduction in stay in hospital of the trifluoperazine-treated patient is due to the quicker response to trifluoperazine. In the figures of trifluoperazine-treated patients for 1959–1960, not referred to in this article, it was found that by the initial use of intramuscular trifluoperazine response has been speeded up and length of stay in hospital further reduced.

The above figures are closely comparable to those given by Macdonald and Watts (1959).

We are of the opinion that trifluoperazine is as effective in hebephrenic schizophrenia as in paranoid schizophrenia and our figures show that more hebephrenics than paranoids were treated with equally good results.

			TABLE V		
			Not Improved	Improved	Improved
Hebephrenics	..	..	5	35	87·5
Paranoids	..	..	5	26	83·8

It might be mentioned here that the three catatonic schizophrenics treated with trifluoperazine responded well to treatment. Unfortunately, not enough cases in any one sub-group of schizophrenics have as yet been treated to make a valid statistical analysis.

SUMMARY

A comparison has been made between the effects of trifluoperazine and I.C.T. in schizophrenics of less than two years duration.

The proportion of patients improved was significantly higher in the trifluoperazine-treated group than in the I.C.T. group.

The relapse rate of I.C.T. patients was higher than that of the trifluoperazine-treated group.

The mean duration of stay in hospital was significantly less in trifluoperazine-treated patients.

It would seem that trifluoperazine is equally effective in hebephrenic and paranoid schizophrenics of recent onset.

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DISCREPANCIES BETWEEN THE PATTERN OF ABILITIES FOR NORMAL AND NEUROTIC CHILDREN

By

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INTRODUCTION

IN the WISC manual Wechsler (1949) gives correlation matrices for his battery of 12 cognitive tests for three random samples of normal children aged $7\frac{1}{2}$, $10\frac{1}{2}$ and $13\frac{1}{2}$ years respectively. A factor analysis of each of these matrices, excluding the *information* and *mazes* tests which are seldom used in Britain, is reported elsewhere (Maxwell, 1959), and it is shown that the pattern of loadings is similar for all three age groups. The question then arose as to how the pattern of loadings for a sample of children attending a psychiatric clinic would compare with that obtained for normal children. The problem is investigated in this article.

THE SAMPLE

From the files of the Bethlem Royal and Maudsley Hospital children's department all children born in the years 1944, 1945 and 1946, for whom complete scores (first administration) on the 10 subtests of the WISC listed in Table II were extracted. This yielded a sample of children ranging in age from .8 to 13 years inclusive as shown in Table I.

TABLE I

Children by Age and Sex for Whom Complete Scores on Ten Tests of the WISC were Available

Age in Years						Boys	Girls	Total
Not recorded	..	..	..	..	..	5	—	5
8 ..	..	..	..	..	..	5	3	8
9 ..	..	..	..	..	..	37	8	45
10 ..	..	..	..	..	..	50	24	74
11 ..	..	..	..	..	..	51	23	74
12 ..	..	..	..	..	..	46	23	69
13 ..	..	..	..	..	..	11	6	17
Total	..	..	..	..	..	205	87	292
Average age	..	..	..	..	..	10.6	10.8	

The majority of these children had been referred to the clinic because of behaviour disorders—stealing, lying, truancy, temper tantrums, aggressiveness, anxiety states, enuresis, sleep walking, etc. But the sample also contained a small percentage of epileptics and brain-damaged children and a few who were possibly mentally defective. As a diagnosis for all the children was not available an exact statement of the cause of referral for the full sample of 292 children cannot be given.

THE DATA

Both the raw scores and the "scaled scores" (mean=10, S.D.=3) for each child on each test were tabulated. The raw scores were used when finding the correlations between the tests but the means and standard deviations given in Table II are for the "scaled" scores. These were chosen because standard deviations for "scaled" scores for samples of normal children are reported in the WISC manual thus enabling a comparison between the standard deviations for the normal and the experimental groups to be made.

TABLE II
Means and Standard Deviations

	Boys (205)		Girls (87)		Boys and Girls	Wechsler's 10½-Year Olds (200)	F-ratio
	Mean	S.D.	Mean	S.D.	S.D.	S.D.	
Comprehension ..	<i>9.17</i>	<i>3.46</i>	<i>8.70</i>	<i>3.57</i>	<i>3.49</i>	3.1	<i>1.33</i>
Arithmetic ..	<i>8.69</i>	<i>3.54</i>	<i>8.87</i>	<i>3.51</i>	<i>3.53</i>	3.1	<i>1.30</i>
Similarities ..	<i>10.07</i>	3.19	<i>10.03</i>	<i>3.49</i>	<i>3.28</i>	3.0	1.20
Vocabulary ..	<i>10.12</i>	3.21	<i>9.46</i>	<i>3.40</i>	<i>3.26</i>	3.1	1.11
Digit span ..	<i>8.41</i>	2.93	<i>9.20</i>	<i>3.39</i>	<i>3.07</i>	2.9	1.20
Picture completion	<i>10.44</i>	<i>3.66</i>	<i>9.11</i>	<i>3.50</i>	<i>3.61</i>	3.0	<i>1.45</i>
Picture arrangement	<i>8.97</i>	<i>3.31</i>	<i>8.53</i>	<i>3.56</i>	<i>3.38</i>	3.1	1.19
Block design ..	<i>10.10</i>	<i>3.26</i>	<i>9.30</i>	<i>3.45</i>	<i>3.31</i>	3.0	1.22
Object assembly ..	<i>9.51</i>	<i>3.53</i>	<i>8.45</i>	<i>3.74</i>	<i>3.59</i>	2.9	<i>1.53</i>
Coding ..	<i>7.44</i>	3.23	<i>8.37</i>	<i>3.47</i>	3.30	3.1	1.13

(Means italicized differ significantly from the expected values of 10; S.D.s from the expected value of 3; the F-ratios italicized are significant beyond the 5 per cent. level.)

An examination of the means in Table II shows that, with the exception of the girls' mean on Similarities and the boys' means on the same test, and on Vocabulary, Picture Completion and Block Design, all the means are below the expected value of 10 (for normal children), some of them—Coding for instance—being noticeably so. Since the population standard deviation of each test is 3 a deviation of 0.63 in the case of girls (N=87), and 0.41 in the case of boys (N=205), on either side of the mean of 10 would represent a significant difference at the 5 per cent. level. On these criteria the means underlined differ significantly from the expected values for normal children, all—except that for Picture Completion for boys—being below these values. From these results it seems that the sample of psychiatric children, whatever the reasons, obtain on the average lower scores on the WISC tests than do normal children.

In Table II the standard deviations of the scores are also given—separately for boys and girls and then for the sexes combined. When the latter (the average age of the sample being 10½ years) are tested against the standard deviations for Wechsler's 10½-year old normal sample, reproduced for convenience in Table II, four of the F-ratios of the variances are found to be significant. These are for Comprehension, Arithmetic, Picture Completion and Object Assembly. Closer examination of the standard deviations, however, shows that those for our sample are consistently greater than those for Wechsler's. To emphasize this point each standard deviation was now tested against its population value of 3, by the appropriate chi-square test, and in cases where

the difference was found to be significant the value was italicized. The italicized values in Table II show that whereas none of the standard deviations for Wechsler's data differs from its expected value, all the standard deviations for our sample, with the exception of that for Digit Span, do differ from their expected values. From these results we may conclude that, though the scores for Wechsler's sample cannot be considered to depart significantly from the population values as regards dispersion, those for our sample of psychiatric children do. It is well too to note that ours is a highly selected sample where the population at large is concerned, and that children who were too dull or too mentally disturbed to complete all 10 tests of the battery were excluded from it. This means that the standard deviations we obtained may underestimate the true values for the population of children who require psychiatric help. It would appear then that the dispersion of scores in the latter population is greater for the tests in question than it is for normal children.

THE CORRELATIONS

The intercorrelation of the ten tests for our combined sample of 292 children were now found, and are given in Table III. They were obtained from the raw, rather than the scaled, scores to avoid possible contamination due to transformation; though Wechsler states that the scaled scores are obtained from his raw scores by a direct linear transformation and so would not have affected the magnitude of his correlations the same would not necessarily be true for our data. When the correlations in Table III are compared with those for normal

TABLE III
The Intercorrelations of Ten Subtests for Sample of 292 Children

	Arith- metic	Similar- ities	Vocab- ulary	Digit Span	Picture Com- pletion	Picture Arrange- ment	Block Design	Object As- sembly	Cod- ing
Comprehension ..	0.618	0.716	0.713	0.512	0.634	0.645	0.476	0.556	0.606
Arithmetic ..		0.687	0.617	0.587	0.551	0.603	0.650	0.503	0.636
Similarities ..			0.743	0.479	0.582	0.627	0.566	0.572	0.607
Vocabulary ..				0.539	0.638	0.634	0.577	0.595	0.600
Digit span ..					0.449	0.494	0.463	0.429	0.511
Picture completion ..						0.673	0.635	0.677	0.615
Picture arrangement ..							0.605	0.674	0.648
Block design ..								0.682	0.627
Object assembly ..									0.613

children given by Wechsler they are seen to be considerably and consistently larger—the average increase is about 60 per cent. The differences too are almost everywhere significant. Greater correlations for our sample, of course, were expected since our standard deviations are the larger, but examination of the distributions of the scores showed them to be remarkably normal—with slight deficiencies in the tails—so that the larger correlations cannot be explained away in terms of bimodality or skewness. The larger age range in our sample than in Wechsler's samples however, may be partly responsible for the larger correlations and this point will be investigated in a further study.

FACTOR ANALYSIS

The matrix of correlations, Table III, was now factor analysed using the Mercury Programme (Nixon, and Maxwell 1960) for Lawley's maximum

likelihood method of analysis. After three factors had been fitted a chi-square test on the residuals showed them to be still significant, though only just at the 5 per cent. level. However, an estimate of the loadings for a fourth factor revealed that they were uniformly low and in all would extract only 1 per cent. of the total variance so the analysis was not continued further. A factor analysis of Wechsler's correlation matrix for 10½-year-old boys and girls has already been reported (Maxwell, 1959) and these loadings are given in Table IV for easy comparison.

When the factors for the two samples are examined the striking feature is the greater percentage of variance extracted by the common factors in the case of our sample (68·9 per cent.) when compared with Wechsler's sample (48·8 per cent.). This was to be expected since our correlations were uniformly

TABLE IV
Unrotated Factor Loadings for 10 WISC Tests for the Psychiatric Sample and Wechsler's 10½ Year Normal Sample

Tests	Psychiatric Sample				Normal Sample		
	I	II	III	h ²	I	II	h ²
Comprehension ..	·778	—·152	—·352	·768	·76	·06	·57
Arithmetic ..	·874	·381	·041	·911	·74	·06	·55
Similarities ..	·814	—·043	—·213	·710	·73	·24	·59
Vocabulary ..	·798	—·170	—·204	·707	·88	·03	·78
Digit span ..	·641	·070	—·042	·418	·54	·02	·29
Picture completion	·755	—·298	·067	·663	·52	—·25	·33
Picture arrangement	·782	—·221	·028	·661	·64	—·12	·42
Block design ..	·767	—·091	·358	·725	·66	—·47	·66
Object assembly ..	·733	—·384	·229	·737	·49	—·49	·48
Coding ..	·771	—·101	·071	·610	·45	·00	·21
Percentage variance	59·81	5·07	4·05	68·93	42·8	6·0	48·8

greater than his. The greatest discrepancy between the studies is on factor I where our first factor extracts 59·8 per cent. of the total variance as compared with 42·8 per cent. for his. Most of this increase comes from increased loadings for the last five—the so-called “performance” tests—for the psychiatric sample.

To facilitate further comparison of the two sets of results the factors for the psychiatric sample, Table IV, were rotated—the rotated loadings are given in Table V—so that the Vocabulary test had zero loadings on factors II and III. As a result the first factor is heavily loaded on the verbal side, but as it is also a general factor it is best to label it *verbal-intellectual*. It still extracts much more variance in the case of the psychiatric sample than it does in the case of the normal sample, where the first factor had also been interpreted as a “verbal-intellectual” factor. On the second factor, which may be labelled *space-performance* in view of its high loadings on Block Design and Object Assembly, moderate discrepancies between the loadings for the two samples are found on the similarities and coding tests, but otherwise the loadings are very alike. The third factor has its highest loadings on Arithmetic and Digit Span. It is known (Davis, 1956) that the Digit Span test is a good measure of “fluency” and “uninhibitedness” and this finding may well reflect the tendency towards aggressiveness often observed in children attending a psychiatric clinic.

TABLE V

Rotated Factor Loadings for Psychiatric Sample and Loadings for Wechsler's Sample with Signs on Factor II Reversed

Tests	Psychiatric Sample			Wechsler's Sample	
	I	II	III	I	II
Comprehension ..	·864	—·146	·025	·76	—·06
Arithmetic	·742	·256	·544	·74	—·06
Similarities	·833	·005	·130	·73	—·24
Vocabulary	·841	·000	·002	·88	—·03
Digit span	·604	·118	·197	·54	—·02
Picture completion ..	·761	·252	—·146	·52	·25
Picture arrangement	·780	·221	—·063	·64	·12
Block design	·659	·537	·044	·66	·47
Object assembly	·718	·404	—·243	·49	·49
Coding	·734	·260	·050	·45	·00
Percentage variance	57·4	7·3	4·4	42·8	6·0

PSYCHIATRIC VARIABLES

It is often claimed that social conditions, child-parent relationships, sibling rivalry and such factors influence the results obtained by children on intelligence tests. To enable some estimate of the effect of such factors to be made seven "psychiatric" variables, in which the psychiatrists in charge were particularly interested, were included. They were:

1. Maternal solicitude or anxiety greater than average;
2. Maternity solicitude or anxiety less than average;
3. Paternal lack, due to death, divorce, etc. before the age of five;
4. Paternal lack after the age of five;
5. Parental over-restriction;
6. Disturbances of function (alimentary, enuretic, parosis, hyperactivity, tics, sleep, eating);
7. Disturbed family or social relationships (parental, school, sibling rivalry).

As the data for these variables were dichotomous, associations between them and the cognitive variables were tested by dichotomizing the latter at their medians and performing chi-square tests. The few chi-square values which reached a reasonable level of significance are shown in Table VI. The signs in the table indicate the directions of the associations; for example, a minus sign indicates that an above average score on a test tends to be associated with the absence of the psychiatric variable, and *vice versa*; while a positive sign indicates that an above average score on the test tends to be associated with the presence of the psychiatric variable, and *vice versa*.

Turning now to Table VI we see that psychiatric variable 4, namely "paternal lack after the age of five" is negatively associated with five of the tests, a finding which is complimentary to fathers. Variable 2, namely "maternal solicitude or anxiety less than average" is negatively associated with the Picture Completion test, a finding which indicates that lack of interest on the part of the mother has an adverse effect on the child's performance on the test. On the other hand variable 7, that is "disturbed family and social relationships", is positively associated with two of the cognitive tests namely Block Design

TABLE VI

Chi Square Values with Signs Showing the Direction of the Associations Between the Psychiatric and Cognitive Variables

Cognitive Variables	1	2	3	4	5	6	7
Comprehension ..				-7.75			
Vocabulary				-3.72			
Picture completion				-4.59	4.94		
Picture arrangement	5.18	-6.83		-3.56			
Block design ..							4.25
Object assembly ..							5.19
Coding				-4.41			

(A chi-square of 3.84 is significant at 5 per cent. level, one of 6.63 is significant at 1 per cent. level.)

and Object Assembly, indicating that the presence of such disturbed relationships tends to increase children's scores on these tests—a strange thing! Two further positive associations exist, involving the variables “maternal solicitude or anxiety greater than average” and “paternal over-restriction”, and the tests Picture Arrangement and Picture Completion respectively. But apart from these few significant associations the children's performance on the cognitive tests seems not to be affected by the “psychiatric” variables. It may be well too to note that even in cases where significant associations exist their effect on the correlations between the tests, which is a problem of considerable interest in this article, are slight. For instance if we adjust the correlation of 0.682 between the tests Object Assembly and Block Design to eliminate the effect of the significant associations of like sign between them and psychiatric variable 7, the adjusted value is 0.674, so that the change in the correlation is negligible. Here we may note that had the two associations concerned been of unlike sign the correlation would have been increased rather than decreased after adjustment. It appears then that, provided the seven psychiatric variables included in this study are representative of such variables, the possibility of accounting in terms of such variables for the large differences between the intercorrelations of the cognitive tests, for our sample of children from the clinic and a normal sample, is remote.

BRITISH NORMS FOR THE WISC

When seeking an explanation of the apparently greater dispersion and intercorrelation of test scores for our psychiatric sample, as compared with a normal sample, it must be remembered that the WISC battery of tests has not been standardized for British children. Consequently the comparisons made above between our data and Wechsler's are, to a greater or less extent, suspect. However, some information about the performance of normal British children on the WISC is available. Jones (1959) reports data for three stratified samples of 80 children each—boys and girls in equal numbers—of 8, 9 and 10-year-old London children. She found that whereas the means of the standard scores on the separate tests for her samples tended to be greater than the expected values of 10, the standard deviations tended to be considerably lower than the expected values of 3. In addition the intercorrelations of the test scores for her samples were also lower, especially for the so-called “Verbal” tests, than those given in the test Manual. Mean scores somewhat similar to those reported by Jones were also found—for 10-year-old British, as distinct from London,

children—in an investigation carried out by the Committee of Professional Psychologists, but the standard deviations were on the average similar to Wechsler's. Jones attributes the relatively small standard deviations which she obtained to the uniformity of instruction and of teaching methods within the L.C.C. schools from which her samples were drawn. However, the bulk of the children in our psychiatric sample come from similar L.C.C. schools and this would appear to support the contention that a real difference in the dispersions and intercorrelations of the WISC tests does exist between psychiatric and normal children. Critics, who are sceptical that this is so, have rightly pointed out the possibility that our psychiatric group may be composed of two or more subgroups having different mean scores on the tests. If this were so the combination of such subgroups into one overall group would exaggerate the standard deviations, and possibly the correlation coefficients, obtained. However, under these conditions one would have expected to find bimodality or other signs of non-normality in the test scores and this, as far as can be seen, is not the case. It would appear worth while then to look for some explanation other than those so far considered of the discrepancy in dispersion and intercorrelation of test scores between psychiatric and normal samples and the problem is under investigation.

SUMMARY

Means, standard deviations, correlations and factor loadings for a sample of children attending a psychiatric clinic are reported for the subtests of the WISC, and the results are compared with the normative data given in the WISC Manual and with data for normal British children.

The mean scores for the psychiatric sample, as expected, were found to be lower than those for normal children, but apart from the Coding test—where the decrement is large—the discrepancies were on the average alike for "Verbal" and "Performance" tests. On the other hand the dispersions of the test scores were found to be consistently greater for the psychiatric sample than for the normal samples.

This is a bit surprising for it is reasonable to assume that most children referred to a psychiatric clinic are referred for reasons other than abnormal cognitive development. Because of this they would normally be thought of as providing a "selected" sample where intelligence is concerned and by virtue of such selection should show a dispersion of cognitive tests scores smaller than that obtained in the population at large. This problem requires further investigation.

Due, no doubt, to the greater dispersion of the test scores the intercorrelations of the tests for the psychiatric samples were found to be considerably greater than those for normal children—the "Performance" tests in particular being affected. The effect of these larger correlations shows itself especially in the loadings of the tests on a general factor of ability, which in the psychiatric sample is much more pronounced than it is in the normal sample. It is as well to note, however, that this increased emphasis on a general factor does not imply any diminution of emphasis on the group factors present, as is clear from Table V.

A few interesting associations between cognitive test scores and a number of "psychiatric" variables were also demonstrated. In particular it was seen that the lack of a father in the home tended to have an adverse affect on children's performance on some of the WISC subtests, for example on Comprehension,

Picture Completion and Coding. Other interesting associations, for which ready explanations are not always available, are given in Table VI.

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REACTIONS OF CHILDREN WITHIN FAMILY GROUPS AS MEASURED BY THE BENE-ANTHONY TESTS

By

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From The Society for the Investigation of Human Ecology

THE purpose of this paper is to describe the results obtained when the Bene-Anthony Family Relations Test was administered to 69 children in 28 families and to relate these results to the health and social characteristics of this group. These children, 17 American Negroes, 46 Puerto Ricans and 6 Americans of European descent receive out-patient paediatric care from two paediatricians and a public health nurse, in a small family neighbourhood clinic located in a Manhattan slum area. The parents of these children also receive out-patient treatment from the two internists associated with this clinic.

Close contact is maintained with each family and a record is kept of all episodes of illness occurring in each individual whether or not these require medical care. These episodes are counted and evaluated in terms of severity and duration. The number of episodes of illness over a given period of time is used as an index of the individual's health. When individuals are hospitalized summaries of these admissions are included in the family's record. Observations on the day-to-day happenings in the lives of the families studied and the manner in which these people view their situation are also included in the medical record so that clinicians become aware of the setting in which illness occurs. The results obtained through the Bene-Anthony Test provide additional data on the dynamics of family life and on the meaning of illness in this group of children.

METHOD AND PROCEDURE

The Bene-Anthony Test (1, 2) involves 20 outline cardboard figures representing people of various ages, shapes and sizes. Each figure is attached to a little red box with a slot. The test situation is essentially a play situation. The child is asked to pick out a number of figures from this collection to represent the members of his family, including himself. Then he is given little cards which are read to him, or which he may read himself. On these cards are written statements which may apply to different individuals in the family. The child is asked to put the cards "into the person" (hole in the box) whom the message it conveys fits best. If he feels that the statement does not apply to anyone the card is put into a box marked "Mr. Nobody".

While the child is not asked to verbalize his feelings about members of the family, he is expected to express his feelings about himself, his mother, father, and siblings through the choice of a card which states an emotional attitude. The subject puts the card into the hole in the box where it is out of sight, and so he need never compare or sum up his choices. There are two test forms, one with 40 items and a phrasing adapted to a younger age group, the other with a more adult vocabulary including 86 items.

The statements on the cards are designed to elicit the expression of a variety of feelings (2):

1. Positive feelings coming from the child (outgoing), or going towards him (incoming);

i.e. "This person in the family is very nice",—"This person in the family really understands me."

2. Negative feelings coming from the child (outgoing) or going towards him (incoming);

i.e. "This person in the family is sometimes bad-tempered",—"This person in the family hits me a lot."

Another category of feelings is grouped under the heading of "Dependency Feelings". In the form for younger children, dependency items represent the child's feelings of dependency on others; i.e., "N (child's name) wants you to help him get dressed in the morning". "Who should help N get dressed in the morning?"

For older children, the dependency items deal with over-indulgence exercised by either parent or maternal over-protection; i.e., "This is the person in the family father spoils too much"—"Mother worries that this person in the family doesn't eat enough." The figures chosen by the child represent those individuals whom he considers over-indulged or over-protected.

The Paediatrician (M.G.) and the Public Health Nurse (E.J.) administered the test according to the instructions detailed in the manual (2) by the authors of the test. Older children were encouraged to read the cards themselves and enjoyed doing so. Where the children did not understand English, a standard Spanish translation made by the Public Health Nurse was used. Both the Public Health Nurse and the Paediatrician were well acquainted with the children and a good rapport existed between them. The older form was used whenever the examiner felt that the child could comprehend it.

Fifteen boys and seventeen girls—32 children, with a mean age of 5.5 years and an age range of 4–8 years were tested on the shorter form. Thirteen (41 per cent.) were approximately 5 years old. The form for older children was given to 37 subjects—20 boys and 17 girls ranging from 7 to 15 years of age, with a mean age of 10.2 years; 9.9 years for boys, 10.6 years for girls. Twenty, or more than half, were 9 or 10 years old, and only 4 were over 12. With the exception of one child in each group the results from the form for younger children came from individuals of 7 or younger, while the results from the form for older children came from individuals of 8 or older.

On the basis of observations extending over a period of from one to five years, the Internist (B.B.), the Paediatrician (M.G.), and the Public Health Nurse (E.J.), each acting independently, assigned a "good" or "poor" rating to the children tested and to their families on six variables. In a few cases where there was a difference of opinion among the staff, this was resolved by discussion and the rating was revised to represent the opinion of the group.

DEFINITION OF VARIABLES

1. *Health of Child*

A rating of good health was assigned to those children who met the following criteria:

- (a) History of normal development and uncomplicated childhood diseases.
- (b) For the year 1958, eight recorded minor illnesses or less in the case of children under 6; five recorded minor illnesses in the case of children over 6.

Any child with an episode of pneumonia, convulsive disorder, or other serious illness during 1958, was placed in the sicker group.

2. *Health of Family*

The necessary criteria for a rating of good health in the case of the child's family were:

- (a) For the year 1958, a family average of not more than six recorded episodes of minor illness for each member.
- (b) Chronic illness or gross congenital defect in not more than one member of the family.

3. *Quality of Marriage*

Positive evidence of a good relationship between husband and wife as observed by the staff on home visits, in the clinic, and on the street, coupled with lack of evidence that children were used as pawns in domestic quarrels and no report of court procedures between spouses—these formed the basis for a good rating in this category.

4. *Interest of Mother in Children*

The rating was based on evidence of a positive relationship with her children as observed by the staff on home visits, in the clinic, or on the street. Such evidence included:

- (a) Spontaneous demonstrations of affection between parent and child.
- (b) Good verbal communications between them.
- (c) Physical care of child as shown by attention to clothing, meals, and following the doctor's instructions.

Only one of the 28 mothers was felt to lack interest in her children; for the others the contrast is, then, between high and moderate interest.

5. *Interest of Father in Children*

The rating here is between interest and low or no interest. While the same kind of evidence as that found in the case of the mother indicating a positive relationship was used to establish a good rating, the father's role in sharing responsibility for decisions related to education and discipline was considered an important component of his role.

6. *The Father as a Provider*

In this sub-culture the ability for the father to provide for his family is considered his most important characteristic and his position as head of the household in the Puerto Rican family depends on this capacity. For purposes

of this discussion, a father regularly employed who uses his salary for the support of his family was rated as a good provider (3).

Where a man is regularly employed and his earning capacity is low: (i.e. \$40.00 a week) the Department of Welfare grants a supplementary allowance for the support of a large family (3). A father receiving assistance under these circumstances is rated as a good provider by his neighbours; the staff did likewise.

Following the administration of the tests and the assignment of the ratings by the clinical staff, test scores were obtained for each of the 69 children by the Psychologist according to the instructions in the Bene-Anthony Test Manual (2). Then, for each variable, mean test scores of subjects with good and poor ratings were calculated.

Three basic scores were obtained for each figure—Nobody, Father, Mother, Self, and Siblings. These are:

1. The total number of items reflecting *positive* feelings;
2. The total number of items reflecting *negative* feelings;
3. The total number of items reflecting *dependency* feelings.

Two additional scores were derived from these:

- (a) *Total involvement*, which is the sum of the negative and positive items, and represents the amount of the child's emotional investment in the particular family member; and
- (b) *Positive minus negative*, which represents the net amount of positive (or negative) feelings for the family member. The latter score was omitted in the case of Nobody since it has no clear psychological meaning.

In addition, the attitude of each child toward each member was categorized as positive where the sum of *positive* items is more than twice the negative, *negative* where the sum of negative items is more than twice the positive, *ambivalent* where neither the number of positive items nor the number of negative items exceeds two-thirds of their combined number.

The items dealing with siblings were pooled to represent all sibling relationships (see section F in Tables I–VI). Seven subjects, all girls (two older, five younger) included figures not actually in the immediate family. Three of these girls belong to an extended family group that lives in close intimacy, and they included eight cousins, nieces, nephews, and an aunt and uncle in their early teens who are, essentially, sibling figures. The figures added by the other four girls consist of five friends, three cousins, and six adults. All of these figures, with the exception of the adults, were included in the scoring as sibling figures.

The possibility that the pooling of sibling scores might cancel out positive and negative feelings toward individual siblings was considered. On the assumption that the sibling most significant for the subject is the one to whom the greatest number of items have been attributed, the Positive-Negative score for this sibling has been recorded, (See Section G in Tables I–VI.)

The degree and direction of the preference for one parent or the other is indicated through an additional score. This is obtained by subtracting the father's positive-negative score from that of the mother—that is, a positive score represents a preference for the mother and a negative score a preference for the father. (See Section D in Tables I–VI.)

The results are summarized in Tables I through VI. For each variable, the mean test scores of subjects with good and poor ratings are recorded. Mean test scores are presented for boys and girls separately in both the younger and the older age groups. The scores have also been combined under the heading Younger Children and Older Children. Differences between upper and lower groups on each variable were evaluated by the *t*-test, and all values of *t* of 1.00 or greater are shown in the Table.*

Since the two test forms have a different number of items, the test results from older and younger children cannot be combined directly. In some cases, however, a similar trend in relationships appears in both the younger and the older group. In order to ascertain whether a relationship does hold over both age groups either for one sex or for both, each sub-group of subjects was divided at its own median score on the Bene-Anthony Test measure in question. The age groups were then combined and the chi-square test used to determine whether a significant relationship exists between any variable and the likelihood of a child's falling above or below his group's median in any particular test measure.

RELATIONSHIPS BETWEEN TEST AND VARIABLES

Additional findings not described in the tables are reported below. The discussion integrates and interprets these and the principal findings in each table as these relate to each variable.

1. *Health of the Child* (see Table I)

(a) *Additional Findings.* For younger children the items of dependence on Self and on Nobody were combined, since depending on oneself is, in a sense, like depending on nobody. This revealed a significantly greater dependence of the sicker children on "Nobody and Self" (.02 level). The healthier younger children report more dependence on the same sex parent than do the sicker children (.01 level); dependence on the parent of the opposite sex is unrelated to the child's health.

Sixty-seven per cent. of healthier boys exhibit ambivalence as the predominant mode of reaction toward siblings whereas only 18 per cent. of the sicker boys do so (.05 level).

* Since this is an exploratory study and the differences were not predicted, a two-tailed test was used to evaluate the significance level of each *t* (i.e., the probability that such a difference could occur by pure chance). This is the more conservative way of evaluating significance; in future studies, predictions could be made, based on the present results, and one-tailed tests of significance would then be appropriate. Differences that reach the .10 level of significance are cited in the text.

When many *t*-tests are made, as in the present study, a certain number will appear to be significant by chance alone; for example, 10 per cent. of them will reach the 10 per cent. level. Since our interest is in the way that the total pattern of Bene-Anthony Test performance is affected by the six variables being studied, it is useful to test whether the total group of *t*-tests made, or any subgroup of them, is significantly higher than chance. The method used was to compute the number of *t*-values that should reach or exceed 1.00 by chance and compare it with the number actually obtained, using the chi-square test as a one-tailed test (since it is expected that more *t*-values of 1.00 or over would be obtained than chance). This was done for each group of subjects on each variable, and was then used to decide whether to interpret that set of results. In one case, for example, 16 of the 26 values of *t* were 1.00 or more, while the average number expected by chance is 8.7; this would occur by chance only one time in a thousand, so we may interpret the results for that group of subjects on that variable with some confidence. In another instance, only 4 reach a *t* of 1.00 or more, on a chance basis 4 or more such *t*-values would occur 97 times out of 100. In such a case, even if a few results, taken individually, appear to be significant, they should probably not be interpreted, or interpreted with extreme caution.

TABLE I
Health of the Individual Child vs. Bene-Anthony Test Scores
 TEST SCORES

HEALTH OF CHILD	Younger Boys				Younger Girls				Younger Children				Older Boys				Older Girls				Older Children			
	Good	Poor	t		Good	Poor	t		Good	Poor	t		Good	Poor	t		Good	Poor	t		Good	Poor	t	
(A) <i>Nobody:</i>																								
Positive	1.00	0.17	1.58		0.33	0.80			0.62	0.45			2.44	3.91	1.12		6.82	3.17	1.16		4.85	3.65		
Negative	4.22	1.17	1.78†		1.58	2.60			2.71	1.82			13.11	11.00			15.18	7.83	1.44		14.25	9.88		1.30
Total involvement	5.22	1.33	1.96†		1.92	3.40	1.03		3.33	2.27			15.56	14.91			22.00	11.00			19.10	13.53		1.21
Dependency	0.11	1.17	1.07		0.42	1.00			0.29	1.53			3.89	4.09			8.09	2.50	2.50†		6.20	3.53		1.83†
(B) <i>Father:</i>																								
Positive	4.44	2.00	2.16†		2.83	4.20	1.41		3.52	3.00			8.33	7.00			4.09	6.17	1.62		6.00	6.71		
Negative	3.33	3.17			1.75	2.80			2.43	3.00			4.00	6.36			3.64	8.33	1.41		3.80	7.06		1.61
Total involvement	7.78	5.17	1.13		4.58	7.00	1.40		5.95	6.00			12.33	13.36			7.73	14.50	1.83†		9.80	13.76		1.67
Positive-negative	1.11	1.17			1.08	1.40			1.10	0			4.33	0.64			0.45	2.17			2.20	0.35		
Dependency	2.11	0.33	2.95†		0.83	0.80			1.38	0.55	1.84†		1.33	0.64	1.06		0.45	2.67	1.45		0.85	1.35		
(C) <i>Mother:</i>																								
Positive	3.67	5.67	1.71		4.83	3.20	1.35		4.33	4.55			13.00	13.82			11.36	10.00			12.10	12.47		
Negative	2.11	1.17	1.10		3.67	3.20			3.00	2.09	1.08		1.67	2.55			1.09	1.50			1.35	2.18		
Total involvement	5.78	6.83			8.50	6.40			7.33	6.64			14.67	16.36			12.45	11.50			13.45	14.65		
Positive-negative	1.56	4.50	1.84†		1.17	0			1.33	2.45			11.33	11.27			10.27	8.50			10.75	10.29		
Dependency	4.33	3.67			3.75	2.60	1.10		4.00	3.18	1.11		1.00	1.18			0.09	2.50	2.04†		0.50	1.65		1.94†
(D) Positive-negative: Mother-Father	0.44	5.67	2.48†		0.08	1.40			0.24	2.45	1.18		7.00	10.64			9.82	10.67			8.55	10.65		
(E) <i>Self:</i>																								
Positive	1.22	1.83			0.83	2.20	1.56		1.00	2.00	1.37		1.22	1.55			0.18	2.50	1.83†		0.65	1.88		1.86†
Negative	0.33	1.50	1.46		0.83	2.20	1.34		0.62	1.82	1.82†		1.78	1.55			0.36	1.17	1.04		1.00	1.41		
Total involvement	1.56	3.33			1.67	4.40	2.12†		1.62	3.82	1.92†		3.00	3.09			0.55	3.67	1.64		1.65	3.29		1.53
Positive-negative	0.89	0.33			0	0			0.38	0.18			-0.56	0.00			-0.18	1.33	1.88†		-0.35	0.47		
Dependency	0.44	1.00			0.75	2.00	1.32		0.62	1.45	1.32		3.22	4.54			3.64	4.67			3.45	4.59		
(F) <i>Siblings (all siblings):</i>																								
Positive	6.38	7.33			7.25	6.00			6.90	6.80			18.33	12.27	1.17		11.73	12.67			14.70	12.41		
Negative	6.88	9.33	1.44		7.92	6.50			7.50	8.20			13.33	13.18			13.36	14.67			13.35	13.71		
Total involvement	13.25	16.67	1.69		15.17	12.50			14.40	15.00			31.67	25.45	1.04		25.09	27.33			28.05	26.12		
Positive-negative	0.50	2.00			0.67	0.50			-0.60	-1.40			5.00	-0.91			-1.64	-2.00			1.35	-1.29		
Dependency	1.13	1.83	1.08		2.08	2.25			1.70	2.00			12.11	9.91			5.56	10.00	2.10†		8.40	9.94		
(G) <i>Most Involved Sibling:</i>																								
Positive-negative	2.75	2.33			-0.75	0.25			-1.55	1.30			1.00	-1.00			-1.64	-5.83	1.15		-0.45	-2.71		
NUMBER OF CASES	9	6			12	5			21	11			9	11			11	6			20	17		

Note: The entries in this Table represent the mean scores for each group of subjects.

* .01 level (2-tailed) † .05 level (2-tailed) ‡ .10 level (2-tailed)
 Only values of *t* equal to or greater than 1.00 are included in the Table.

When the data for older and younger boys are combined, the sicker boys, regardless of age, give more positive items to the Mother figure ($\cdot 10$ level), and also have a greater total involvement with her ($\cdot 05$ level).

When data for older and younger girls are combined, the converse relationship appears: the sicker girls have a greater total involvement with the Father figure than do the healthier girls ($\cdot 01$ level), and they also ascribe more positive items to him ($\cdot 10$ level). The sicker girls also have greater involvement with the Self figure ($\cdot 02$ level), in which the positive items predominate ($\cdot 01$ level).

(b) *Discussion.* Sicker children, in general, are more highly involved with the parent of the opposite sex than are the healthier children, and this is especially true of positive feelings. The healthier children tend to have more equal attitudes toward both parents. In younger children, where the test provides a more direct statement of the child's dependency relations, we find that healthier children are more likely to rely on the parent of the same sex, while sicker children report fewer sources of help from either parent, relying instead on themselves or on Nobody. The total involvement with Self is greater in the case of all sicker children, but significantly so only for girls. No significant differences were demonstrated between healthier and sicker children in their relationships toward siblings, except that ambivalence is more clearly expressed by healthier boys.

2. Health of Family (see Table II)

(a) *Additional Findings.* All the younger boys from healthier families have a net positive reaction to Self, compared to only 22 per cent. of younger boys from sicker families ($\cdot 01$ level). The former express some dependence on Father (100 per cent. vs. 56 per cent., $\cdot 10$ level), and fewer of them express dependence on any sibling (20 per cent. vs. $\cdot 89$ per cent., $\cdot 05$ level). Younger girls as well as younger boys from healthier families attribute fewer feelings of dependence to Nobody and to Self than do younger children in sicker families ($\cdot 10$ level).

Sixty per cent. of the older boys from healthier families express mixed feelings toward siblings, compared to 20 per cent. of older boys from sicker families ($\cdot 10$ level). When over-protection and over-indulgence items are taken separately, boys from healthier families perceive less over-indulgence from either parent as directed toward the Self figure ($\cdot 02$ level).

When the reactions of both older and younger boys in sicker and healthier families are compared, those from sicker families demonstrate a greater total involvement with the mother ($\cdot 05$ level) a more positive net reaction toward her ($\cdot 05$ level) and a preference for her over the father ($\cdot 10$ level). They give more positive items to Self ($\cdot 02$ level) and have a more positive net reaction to Self ($\cdot 05$ level).

Girls from sicker families contrasted with girls from healthier families have a greater total involvement with Self ($\cdot 05$ level) including a greater number of positive ($\cdot 10$ level) and negative items ($\cdot 02$ level), and also give more positive items to Nobody ($\cdot 02$ level).

(b) *Discussion.* Children in sicker families show a consistent preference for the mother over the father while in healthier families feelings are directed toward both parents equally. The younger children in sicker families are more likely to report a lack of support (i.e. dependence on Self or Nobody).

The family's health also impinges on the children's attitudes toward self.

TABLE II
Health of the Family vs. *Bene-Anthony Test Scores*
TEST SCORES

HEALTH OF CHILD	Younger Boys			Younger Girls			Younger Children			Older Boys			Older Girls			Older Children		
	Good	Poor	t	Good	Poor	t	Good	Poor	t	Good	Poor	t	Good	Poor	t	Good	Poor	t
(A) <i>Nobody:</i>																		
Positive	1.50	0.11	2.04†	0.33	0.63		0.80	0.35	1.16	2.20	4.30†	1.61	3.38	7.44	1.24	2.72	5.79	1.83†
Negative	4.83	1.78	1.14	1.78	2.00		3.00	1.88		10.40	13.50		10.75	14.22		10.56	13.84	
Total involvement	6.33	1.89	1.64	2.11	2.63		3.80	2.24	1.08	12.60	17.80		14.13	21.67		13.28	19.63	1.39
Dependency	0.17	0.78	1.12	0.44	0.75		0.33	0.76	1.13	3.50	4.50		4.63	7.44	1.03	4.00	5.89	1.23
(B) <i>Father:</i>																		
Positive	4.33	2.89	1.13	3.44	3.00		3.80	2.94		8.20	7.00		6.00	3.78	1.60	7.22	5.47	
Negative	2.33	3.89	1.27	1.67	2.50		1.93	3.24	1.40	3.60	7.00	1.35	3.50	6.89	1.08	3.56	6.95	
Total involvement	6.67	6.78		5.11	5.50		5.73	6.18		11.80	14.00		9.50	10.87		10.78	12.42	1.77†
Positive-Negative	2.00	1.00	2.31†	1.78	0.50		1.87	0.29	2.06†	4.60	0		2.50	3.11	1.63	3.67	1.47	
Dependency	1.83	1.11		1.00	0.63		1.33	0.88		1.60	0.30	2.31†	0.88	1.56		1.28	0.89	
(C) <i>Mother:</i>																		
Positive	4.17	4.67		4.11	4.63		4.13	4.65		11.90	15.00	1.00	12.13	9.78		12.00	12.53	
Negative	1.67	1.78		3.56	3.30		2.80	2.59		3.20	1.10	2.09†	1.25	1.22		2.33	1.16	
Total involvement	5.83	6.44		7.67	8.13		6.93	7.24		15.10	16.10		13.38	11.00		14.33	13.68	
Positive-Negative	2.50	2.89		0.56	1.13		1.33	2.06		8.70	13.90	1.61	10.88	8.56		9.67	11.37	
Dependency	4.83	3.56	1.04	3.33	3.50		3.93	3.53		1.30	0.90		0.75	1.11		1.06	1.00	
(D) Positive-Negative: Mother-Father	0.50	3.89	1.41	-1.22	0.63		-0.53	2.35	1.73†	4.10	13.90	1.88†	8.38	11.67		6.00	12.84	1.78†
(E) <i>Self:</i>																		
Positive	1.83	1.22		0.44	2.13	2.72†	1.00	1.65	1.15	2.00	0.80	1.41	0.75	1.22		1.44	1.00	
Negative	0.50	1.00		0.56	2.00	1.80†	0.53	1.47	2.31†	1.30	2.00		1.00	1.00	1.34	0.83	1.53	
Total involvement	2.33	2.22		1.00	4.13	3.08*	1.53	3.12	1.76†	3.30	2.80		1.00	2.22		2.28	2.53	
Positive-Negative	1.33	0.22	1.94†	-0.11	0.13		0.47	0.18		0.70	-1.20		0.50	0.22		0.61	0.53	
Dependency	0.50	0.78		0.56	1.75	1.74	0.53	1.24	1.43	3.20	4.70	1.01	5.50	0.67	1.41	4.22	3.74	1.30
(F) <i>Siblings (all siblings):</i>																		
Positive	5.00	7.78	2.21†	7.89	5.71	1.51	6.86	6.88		18.00	12.00	1.25	12.13	12.00		15.39	12.00	1.15
Negative	8.20	7.78		8.11	6.86		8.14	7.38		15.40	11.10	1.09	17.63	10.44		16.39	10.79	2.08†
Total involvement	13.20	15.56		16.00	12.57	1.11	15.00	14.25		33.40	23.10	1.88†	29.75	22.44		31.78	22.79	2.29†
Positive-Negative	-3.20	0	1.71	-0.22	-1.14		-1.29	-0.50		2.60	0.90		-5.50	1.56		-1.00	-1.21	
Dependency	0.80	1.78	1.25	2.44	1.71		1.73	1.63		11.70	10.10		6.00	7.89		9.17	9.05	
(G) <i>Most Involved Sibling:</i>																		
Positive-Negative	-3.60	-2.00		-0.11	-1.00		-1.36	-1.56		-1.20	0.80		-8.00	1.22	2.96*	-4.22	1.00	1.73†
NUMBER OF CASES	6	9		9	8		15	17		10	10		8	9		18	19	

* .01 level (2-tailed) † .05 level (2-tailed) ‡ .10 level (2-tailed)
Only values of *t* equal to or greater than 1.00 are included in the Table.

Girls from sicker families show a greater total involvement with Self in contrast to boys from the same families who have a negative attitude toward Self.

Some relationships are manifest only in older children. More items, especially positive ones, are assigned to Nobody in sicker families—suggesting that these children direct fewer positive feelings toward any member of the family. In healthier families both boys and girls are greatly involved with siblings, the boys indicating ambivalent feelings, the girls expressing hostility. In sicker families there appears to be a withdrawal from such involvement particularly in the area of positive feelings.

3. *Quality of Marriage* (see Table III)

(a) *Additional Findings.* For younger children no relationships of statistical significance are associated with this variable, but a few relationships hold true for the entire sample regardless of age or sex—when the data for children from more adequate marriages are compared with those from less adequate marriages, in the former case, more items both positive and negative are assigned to the mother ($\cdot 10$ level). A more positive net reaction is expressed toward the father ($\cdot 05$ level) and a more negative net reaction is directed toward the sibling with whom the child is most strongly involved ($\cdot 05$ level). When the data for older boys of more adequate marriages are analysed separately, these boys attribute fewer dependency items dealing with over-indulgence to Nobody ($\cdot 01$ level). This trend holds when the data for older boys and girls from more adequate marriages are combined and compared with the data for older children of less adequate marriages.

(b) *Discussion.* The fact that the quality of the marriage does not affect the test results in younger children is worthy of note since younger children are affected by characteristics of the mother and father separately as evidenced by the scores obtained for the variables dealing with the parents' concern for their children and the father's adequacy as a provider.

These characteristics of the parents impinge directly on the child's life and it is possible that the relationship of the parents to each other becomes meaningful only as the child grows older.

For older children, the preference for the mother over the father is marked where the marriage is less adequate. The quality of the marriage does not affect boys' attitudes toward the father, and the girls' attitude toward the mother is not affected. But in poor marriages, boys express positive attitudes towards the mother almost exclusively and the girls show a marked shift of negative feelings toward the father, while both boys and girls feel that the parents are less likely to over-indulge any member of the family.

Where the marriage is good, the attitudes towards both parents are positive and fairly similar, and boys allow some negative feelings to be expressed toward the mother.

While more negative attitudes are expressed toward siblings when the data for all siblings are added together, there is a trend for the sibling with whom the child is most involved to be strongly disliked but for primarily positive feelings to be expressed toward other children in the family. The children of less adequate marriages show no such clear contrast, but express more positive feelings toward all siblings.

TABLE III
Adequacy of Marriage vs. *Bene-Anthony Test Scores*
TEST SCORES

HEALTH OF CHILD	Younger Boys			Younger Girls			Younger Children			Older Boys			Older Girls			Older Children		
	Good	Poor	t	Good	Poor	t	Good	Poor	t	Good	Poor	t	Good	Poor	t	Good	Poor	t
(A) <i>Nobody:</i>																		
Positive ..	1.00	0.38	1.06	0.70	0.17	1.06	0.82	0.29	1.40	3.56	3.00		6.00	5.83		4.31	4.62	
Negative ..	4.14	2.00	1.30	2.60	1.00	1.30	3.24	1.57	1.53	8.67	15.78	1.46	12.00	13.75		9.69	14.62	1.48
Total involvement ..	5.14	2.38	1.08	3.30	1.17	1.64	4.06	1.86	1.69†	12.22	18.78	1.16	18.00	19.58		14.00	19.24	1.12
Dependency ..	0.14	0.88	1.22	0.50	0.83		0.35	0.86		2.22	5.67	2.41†	5.50	6.83		3.23	6.33	2.12†
(B) <i>Father:</i>																		
Positive ..	4.14	2.88		3.60	2.67		3.82	2.79	1.11	6.78	9.67		7.75	3.50	3.21*	7.08	6.14	
Negative ..	2.57	3.88		2.20	1.83		2.35	3.00		4.89	6.11		1.25	6.75	2.43†	3.77	6.48	
Total involvement ..	6.71	6.75		5.80	4.50		6.18	5.79		11.67	15.78	1.10	9.00	10.25		10.85	12.62	1.45
Positive-Negative ..	1.57	1.00	1.93†	1.40	0.83		1.47	0.21		1.89	3.56		6.50	3.25	3.78*	3.31	0.33	1.22
Dependency ..	1.29	1.50		1.20	0.33	1.56	1.24	1.00		0.78	1.00		1.00	1.33		0.85	1.19	
(C) <i>Mother:</i>																		
Positive ..	4.14	4.75		4.00	5.50		4.06	5.07		10.56	15.67	1.61	9.25	11.67		10.15	13.38	1.54
Negative ..	1.71	1.75		3.10	4.33		2.53	2.86		3.00	1.22	1.53	1.00	1.17		2.38	1.19	1.46
Total involvement ..	5.86	6.50		7.10	9.83	1.03	6.59	7.93		13.56	16.89		10.25	12.83		12.54	14.57	
Positive-Negative ..	2.43	3.00		0.90	1.17		1.53	2.21		7.56	14.44	2.05†	8.25	10.50		7.77	12.19	1.93†
Dependency ..	4.00	4.13		3.60	3.60		3.76	3.86		1.22	1.22		0.50	0.92		1.00	1.05	
(D) <i>Positive-Negative:</i>																		
<i>Mother-Father</i>	0.86	4.00	1.33	-0.50	0.33		0.06	2.43	1.40	5.67	10.89		1.75	13.75	2.80†	4.46	12.52	2.06†
(E) <i>Self:</i>																		
Positive ..	2.29	0.75		1.20	1.50		1.65	1.07		1.89	1.11		0.25	1.33	1.46	1.38	1.24	
Negative ..	1.29	0.38	1.23	0.90	2.00	1.08	1.06	1.07		2.44	1.22		0	0.92	2.30†	1.69	1.05	
Total involvement ..	3.57	1.13	1.59	2.10	3.50		2.71	2.14		4.33	2.33	1.28	0.25	2.25	1.94†	3.08	2.29	
Positive-Negative ..	1.00	0.38		0.30	-0.50		0.59	0		-0.56	-0.11		0.25	0.41		-0.31	0.19	
Dependency ..	1.14	0.25	1.13	1.20	1.17		1.18	0.64		4.56	4.22		2.25	4.33	1.22	3.85	4.29	
(F) <i>Siblings (all siblings):</i>																		
Positive ..	6.17	7.25		7.89	5.67	1.41	7.20	6.57		11.00	19.67	1.69	11.00	12.08		11.00	15.33	1.54
Negative ..	7.67	8.13		8.11	6.83		7.93	7.57		14.44	11.00		18.75	11.17	1.87†	15.77	11.10	1.65
Total involvement ..	13.83	15.38		16.00	12.50	1.04	15.13	14.14		25.44	30.67		29.75	23.25	1.04	26.77	26.43	
Positive-Negative ..	-1.50	-0.88		-0.22	-1.17		-0.73	-1.00		-3.44	8.67	1.78†	-7.75	0.92	2.66†	-4.77	4.24	2.64†
Dependency ..	1.67	1.25		1.89	2.17		1.13	1.36		9.22	12.33	1.16	8.25	6.67		8.92	9.10	
(G) <i>Most Involved Sibling:</i>																		
Positive-Negative ..	-2.00	-2.75		-1.44	0.50		-1.80	-1.36		-5.11	4.22	1.94†	-8.25	-1.00	1.72	-6.08	1.24	2.41†
NUMBER OF CASES ..	7	8		10	6		17	14		9	9		4	12		13	21	

† .05 level (2-tailed)
‡ .10 level (2-tailed)
* .01 level (2-tailed)
Only values of t equal to or greater than 1.00 are included in the Table.
NOTE: The entries in this Table represent the mean scores for each group of subjects.

Note: The entries in this Table represent the mean scores for each group of subjects.

* .01 level (2-tailed) † .10 level (2-tailed)
Only values of t equal to or greater than 1.00 are included in the Table.

4. *Interest of Mother in Children* (see Table IV)

(a) *Additional Findings.* Older girls with more interested mothers attributed fewer dependency items to Nobody, and this is most marked for items dealing with maternal over-protection ($\cdot 01$ level). The qualitative aspects of dependency are brought out in the analysis of the items relating to maternal over-indulgence. This, they perceive as directed toward siblings ($\cdot 05$ level) and their mother appears as the recipient of paternal over-indulgence ($\cdot 10$ level). When the data for older children are combined, those with more interested mothers perceive less parental (maternal-paternal) over-indulgence as directed toward Nobody; a greater number of items in this category are assigned to siblings ($\cdot 02$ level) and they are more likely to have their greatest involvement with a younger sibling ($\cdot 05$ level).

In the case of older and younger boys, the sons of more interested mothers give more negative items to the Mother figure and, as a result, have a less positive net reaction to her. Older and younger girls of more interested mothers on the other hand have a greater total involvement with all siblings both in regard to positive ($\cdot 05$ level) and to negative items ($\cdot 05$ level). Their most frequent reaction to siblings is more likely to be ambivalent ($\cdot 10$ level) and less likely to be positive ($\cdot 10$ level).

(b) *Discussion.* This is one of the two variables yielding the fewest significant relationships with the Bene-Anthony Test, the other being Adequacy of Marriage, where relationships were limited to older children.

The group of mothers, as already noted, did not vary much in their degree of interest in their children: 12 were considered to show high interest; 15, high-average interest; and only one mother was felt to be definitely uninterested in her children. In general, the largest families were those with younger children, and they were also those with the most interested mothers. This finding for this particular group substantiates the clinical impression of the physicians and the nurse.

In the case of younger children where the mother's interest is low, the girls are much more involved with her both positively and negatively. The boys, on the other hand, tend to suppress negative feelings toward her, and to over-value her in comparison with the father. Their greater report of dependence on Nobody, since it is not coupled with greater dependence on Self, seems to reflect a feeling that help is unavailable, rather than self-reliance.

The significant relationships are concentrated in the group of older girls and are of interest as they may reflect the kind of identification with the mother's role which arises in association with different kinds of mothers, even when differences among these are slight. Yet one profile stands out clearly, the older girl of a loving mother who is developing a benign conception of the mother's role, has a positive and balanced attitude toward both parents, interests herself in a younger sibling, does not suppress mixed feelings about other siblings, and is developing her own self esteem.

5. *Interest of Father in Children* (see Table V)

(a) *Additional Findings.* For younger boys, when the difference in dependence on the two parents is compared, those with more interested fathers rely about equally on both parents, while those with less interested fathers rely almost exclusively on the mother ($\cdot 10$ level).

For the entire sample, children whose fathers are more interested attribute

TABLE IV
Mother's Interest in Children vs. Bene-Anthony Test Scores
TEST SCORES

HEALTH OF CHILD	Younger Boys			Younger Girls			Younger Children			Older Boys			Older Girls			Older Children		
	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t
(A) <i>Nobody:</i>																		
Positive	1.11	0	2.30†	0.71	0.30		0.94	0.19	2.14†	3.50	3.00		1.00	6.50	2.47†	2.92	5.04	1.37
Negative	3.56	2.17		1.71	2.00		2.75	2.06		11.80	12.10		5.33	14.14	1.57	10.31	13.29	1.13
Total Involvement	4.67	2.17	1.19	2.43	2.30		3.69	2.25	1.04	15.30	15.10		6.33	20.64	1.93†	13.23	18.33	1.09
Dependency	0.11	1.17	1.39	0.29	0.80	1.13	0.19	0.94	1.96†	3.20	4.80	1.00	1.67	7.07	2.38†	2.85	6.13	2.38†
(B) <i>Father:</i>																		
Positive	3.56	3.33		2.57	3.70		3.13	3.56		6.20	9.00		7.33	4.29	2.14†	6.46	6.25	
Negative	2.44	4.50	1.13	1.71	2.30		3.13	3.13	1.03	3.80	6.80	1.19	4.00	5.57		3.85	6.08	1.36
Total Involvement	6.00	7.83		4.29	6.00		5.25	6.69		10.00	15.80	1.69	11.33	9.86		10.31	12.33	
Positive-Negative	1.11	1.17	1.59	0.86	1.40		1.00	0.43		2.40	2.20		3.33	1.28	1.63	2.61	0.17	1.10
Dependency	1.22	1.67		0.90	0.80		1.03	1.13		0.80	1.10		1.33	1.21		0.92	1.17	
(C) <i>Mother:</i>																		
Positive	4.00	5.17		2.57	5.60	2.15†	3.38	5.44	2.07†	12.80	14.10		9.00	11.29		11.92	12.46	
Negative	2.33	0.83	2.14†	2.00	4.60	1.99†	2.19	3.19	1.11	2.20	2.10		2.00	1.07	1.39	2.15	1.50	
Total Involvement	6.33	6.00		4.57	10.20	2.59†	5.56	8.63	2.14†	15.00	16.20		11.00	12.36		14.08	13.96	
Positive-Negative	1.67	4.33	1.81†	0.57	1.00		1.19	2.25	1.00	10.60	12.00		7.00	10.22		9.77	10.96	
Dependency	4.22	3.83		3.60	3.30		3.94	3.50		1.00	1.20		1.67	0.79	1.00	1.15	0.96	
(D) <i>Positive-Negative:</i>																		
<i>Mother-Father</i>	0.56	5.50	2.56†	-0.29	-0.40		0.19	1.81		8.20	9.80		3.67	11.50	2.00†	7.16	10.79	1.04
(E) <i>Self:</i>																		
Positive	1.78	1.00		1.00	1.40		1.44	1.25		1.90	0.90	1.16	1.67	0.86		1.85	0.87	1.74†
Negative	1.00	0.50		1.14	1.30		1.06	1.00		2.20	1.10		0	0.79	2.24†	1.69	0.92	
Total Involvement	2.78	1.50		2.14	2.70		2.50	2.25		4.10	2.00	1.44	1.67	1.64		3.54	1.79	1.42
Positive-Negative	0.78	0.50		-0.14	0.10		0.38	0.25		-0.30	-0.20		1.67	0.07	1.27	0.16	-0.05	
Dependency	1.11	0	1.88†	1.00	1.20		1.06	0.75		3.50	4.40		3.00	4.21		3.38	4.29	
(F) <i>Siblings (all siblings):</i>																		
Positive	7.50	5.83	1.20	9.00	5.33	2.77†	8.20	5.53	2.90*	11.50	18.50	1.48	14.67	11.50		12.23	14.42	
Negative	7.88	8.00		9.43	6.11	1.86†	8.60	6.87	1.35	13.40	13.10		22.00	12.07	2.20†	15.38	12.50	
Total Involvement	15.38	13.83		18.43	11.44	2.43†	16.80	12.40	2.37†	24.90	31.60	1.16	36.67	23.57	1.63	27.62	26.92	
Positive-Negative	0.38	2.17		-0.43	-0.78		-0.40	-1.33		1.50	5.40	1.09	-7.33	-0.57	2.83†	-3.15	1.92	1.40
Dependency	1.50	1.33		2.43	1.67		1.93	1.67		11.60	10.20		10.00	6.36	1.21	11.23	7.96	1.83†
(G) <i>Most Involved Sibling:</i>																		
Positive-Negative	2.56	2.17		-1.57	0.33		-2.27	-0.67	1.13	-0.90	0.50		-10.67	-1.50	3.38*	-3.15	-0.67	
NUMBER OF CASES	9	6		7	10		16	16		10	10		3	14		13	24	

NOTE: The entries in this Table represent the mean scores for each group of subjects.

* .01 level (2-tailed) † .05 level (2-tailed) ‡ .10 level (2-tailed)
Only values of t equal to or greater than 1.00 are included in the Table.

TABLE V
Father's Interest in Children vs. Bene-Anthony Test Scores
 TEST SCORES

HEALTH OF CHILD	Younger Boys						Younger Girls						Older Boys						Older Girls						Older Children					
	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t	High	Low	t
(A) <i>Nobody:</i>																														
Positive	1.00	0.38		0.54	0.33		0.70	0.36		3.45	3.00		3.45	3.00		3.75	6.58		3.53	5.26		3.53	5.26		3.53	5.26		3.53	5.26	
Negative	5.00	1.25	1.92†	2.15	1.33		3.85	1.27	1.80†	9.36	16.71	1.33	9.36	16.71	1.33	10.75	14.17		9.73	15.11		9.73	15.11		9.73	15.11		9.73	15.11	
Total involvement	6.00	1.63	1.86†	2.69	1.67		3.85	1.64	1.86†	12.82	19.71	1.16	12.82	19.71	1.16	14.50	20.75	1.06	13.27	20.37		13.27	20.37		13.27	20.37		13.27	20.37	
Dependency	0.57	0.50		0.38	1.67	1.06	0.45	0.82		2.64	6.00	2.15†	2.64	6.00	2.15†	5.25	6.92		3.33	6.58		3.33	6.58		3.33	6.58		3.33	6.58	
(B) <i>Father:</i>																														
Positive	5.29	1.88	3.24*	3.54	2.00		4.15	1.91	2.93*	7.45	9.43		7.45	9.43		7.50	3.58	2.68†	7.47	5.74		7.47	5.74		7.47	5.74		7.47	5.74	
Negative	3.43	3.13		2.00	2.33		2.50	2.91		4.91	6.43		4.91	6.43		1.50	6.67	2.21†	4.00	6.58		4.00	6.58		4.00	6.58		4.00	6.58	
Total involvement	8.71	5.00	1.50	5.54	4.33		6.65	4.82	1.38	12.36	15.86		12.36	15.86		9.00	10.25		11.47	12.32		11.47	12.32		11.47	12.32		11.47	12.32	
Positive-Negative	1.86	1.25	2.54†	1.54	0.33		1.65	1.00	2.32†	2.55	3.00		2.55	3.00		6.00	3.08	3.16*	3.47	0.86		3.47	0.86		3.47	0.86		3.47	0.86	
Dependency	2.14	0.75	1.71	0.92	0.67		1.35	0.73	1.47	0.64	1.29		0.64	1.29		1.25	1.25		0.80	1.26		0.80	1.26		0.80	1.26		0.80	1.26	
(C) <i>Mother:</i>																														
Positive	4.14	4.75		3.77	8.00	1.60	3.90	5.64	1.60	11.45	15.71	1.11	11.45	15.71	1.11	10.25	11.33		11.13	12.95		11.13	12.95		11.13	12.95		11.13	12.95	
Negative	1.86	1.63		3.38	4.33		2.85	2.36		2.91	0.86		2.91	0.86		0.75	1.25		2.37	1.11		2.37	1.11		2.37	1.11		2.37	1.11	
Total involvement	6.00	6.38		7.15	12.33	1.43	6.75	8.00		14.36	16.57	2.01†	14.36	16.57	2.01†	11.00	12.38		13.57	14.05		13.57	14.05		13.57	14.05		13.57	14.05	
Positive-Negative	2.29	3.13		0.38	3.67	1.62	1.05	3.27	1.80†	8.55	14.86	1.70	8.55	14.86	1.70	0.50	10.08		8.80	11.84		8.80	11.84		8.80	11.84		8.80	11.84	
Dependency	3.29	4.75	1.37	3.54	3.67		3.45	4.45	1.25	1.00	1.57		1.00	1.57		0.50	0.83		0.87	1.16		0.87	1.16		0.87	1.16		0.87	1.16	
(D) Positive-Negative: Mother-Father	0.43	4.38	1.76†	-1.15	4.00	1.30	-0.60	4.27	2.82*	6.00	11.86		6.00	11.86		3.50	13.17	1.91†	5.33	12.68		5.33	12.68		5.33	12.68		5.33	12.68	1.87†
(E) <i>Self:</i>																														
Positive	2.14	0.88	1.31	1.38	1.00		1.65	0.91	1.40	1.64	1.29		1.64	1.29		0.25	1.33	1.46	1.27	1.32		1.27	1.32		1.27	1.32		1.27	1.32	
Negative	1.14	0.80		1.15	2.00		1.15	0.91		2.18	1.29		2.18	1.29		0.25	0.83	1.22	1.67	1.00		1.67	1.00		1.67	1.00		1.67	1.00	
Total involvement	3.29	1.38	1.19	2.54	3.00		2.80	1.82	1.01	3.82	2.57		3.82	2.57		0.50	2.17	1.58	2.93	2.32		2.93	2.32		2.93	2.32		2.93	2.32	
Positive-Negative	1.00	0.38		0.23	1.00		0.50	0		-0.55	0		-0.55	0		0	0.50		-0.40	0.32		-0.40	0.32		-0.40	0.32		-0.40	0.32	
Dependency	1.14	0.25	1.14	1.46	0	5.01*	1.35	0.18	2.98*	5.00	3.43	1.03	5.00	3.43	1.03	2.50	4.25	1.07	4.33	3.95		4.33	3.95		4.33	3.95		4.33	3.95	
(F) <i>Siblings (all siblings):</i>																														
Positive	5.67	7.63	1.43	7.58	4.67	1.24	6.94	6.81		12.73	19.43	1.07	12.73	19.43	1.07	12.25	11.67		12.60	14.53		12.60	14.53		12.60	14.53		12.60	14.53	
Negative	5.67	0.63	2.72†	8.00	6.00		7.22	8.64	1.01	14.81	9.43	1.23	14.81	9.43	1.23	19.50	10.92	2.35†	16.07	10.37		16.07	10.37		16.07	10.37		16.07	10.37	2.10†
Total involvement	11.33	17.25	3.37*	15.58	10.67		14.17	15.45		27.55	28.86		27.55	28.86		31.75	22.58	1.61	28.67	24.89		28.67	24.89		28.67	24.89		28.67	24.89	2.14†
Positive-Negative	0	-2.40		-0.42	-1.33		-0.28	-1.82	1.14	-2.09	10.00	1.40	-2.09	10.00	1.40	-7.25	0.75	2.80†	-3.97	9.16		-3.97	9.16		-3.97	9.16		-3.97	9.16	
Dependency	1.00	1.75		2.00	2.00		1.67	1.82		9.27	13.14	1.21	9.27	13.14	1.21	8.00	6.75		8.93	9.11		8.93	9.11		8.93	9.11		8.93	9.11	
(G) <i>Most Involved Sibling:</i>																														
Positive-Negative	-0.33	-4.25	2.42†	-0.83	0		-0.67	-3.09	1.70†	-1.82	1.71		-1.82	1.71		-10.75	-0.17	4.12*	-4.20	0.53		-4.20	0.53		-4.20	0.53		-4.20	0.53	1.43
NUMBER OF CASES	7	8		13	3		20	11		11	7		11	7		4	12		15	19		15	19		15	19		15	19	

NOTE: The entries in this Table represent the mean scores for each group of subjects.

* .01 level (2-tailed)
 † .05 level (2-tailed)
 ‡ .10 level (2-tailed)
 Only values of *t* equal to or greater than 1.00 are included in the Table.

more positive items to the father ($\cdot 001$ level) and as a result have a more positive net evaluation of the father ($\cdot 001$ level).

Among the younger children, especially girls, of more interested fathers ambivalence towards siblings is the most frequent pattern ($\cdot 05$ level), while older children show a predominantly negative reaction (75 per cent. vs. 26 per cent., $\cdot 01$ level). In the case of older and younger girls, their reaction to the sibling with whom involvement is greatest is negative ($\cdot 05$ level).

(b) *Discussion.* The greater self-reliance expressed by younger girls with interested fathers (and also by younger boys, to a lesser degree) may indicate that such fathers help their younger children toward more mature behaviour. The greater incidence of ambivalent sibling relationships in these children would seem to represent the greater ability to experience mixed feelings toward siblings that is generally found in the healthier family situations.

The older girls with interested fathers also show the greater liking for him and the consequent more equal attitude toward both parents found in younger children.

The most consistent finding throughout the entire sample is that the more interested fathers are much better liked by their children, and that as a result their children express similar feelings toward both parents, rather than strongly favouring the mother.

When the father shows little interest, he is disliked, the mother is preferred and the child depends upon her almost exclusively. Older boys see him as a person who does not indulge the members of the family. Whether this is merely a recognition of the father's actual behaviour or represents something that has become a part of the boys' concept of Self is not clear.

6. *The Father as a Provider* (see Table VI)

(a) *Additional Findings.* The younger boys whose fathers are good providers are more likely to have their greatest sibling involvement with a sister ($\cdot 10$ level): the attitude is positive or mixed. Those whose fathers are poor providers are most involved with a brother: in all cases, the attitude is more than two-thirds negative.

The younger girls whose fathers provide well tend to show ambivalence as their predominant reaction to siblings (91 per cent. vs. $\cdot 0$, significant at $\cdot 01$ level).

Among the older boys of better providers, the significant difference in dependency items given to the Self is related primarily to the items dealing with maternal over-protection ($\cdot 02$ level) and paternal over-indulgence ($\cdot 15$ level), which they see as directed toward themselves. In their relationships with siblings, their greatest involvement is with brothers ($\cdot 05$ level). The older girls in these families report themselves most involved with a brother ($\cdot 10$ level), while those with less adequate fathers are most strongly involved with sisters: when data for older boys and girls are combined, their trend reaches the $\cdot 01$ level.

When the data for older and younger boys are combined, several significant relationships appear. Boys whose fathers are better providers give more positive items to Nobody ($\cdot 10$ level). They have a much higher total involvement with the Father figure ($\cdot 01$ level), which is significant for both positive ($\cdot 10$ level) and negative ($\cdot 05$ level) items. Their net attitude toward the sibling with whom they are most involved is more positive ($\cdot 02$ level). The actual mode of reaction toward this sibling is more likely to be ambivalent ($\cdot 10$ level) and less likely

TABLE VI
Father as a Provider vs. Bene-Anthony Test Scores
TEST SCORES

FATHER'S REACTION TO CHILD	Younger Boys				Younger Girls				Younger Children				Older Boys				Older Girls				Older Children			
	Good	Poor	t		Good	Poor	t		Good	Poor	t		Good	Poor	t		Good	Poor	t		Good	Poor	t	
(A) <i>Not</i> body:																								
Positive	1.11	0	2.30†		0.18	1.20	1.71		0.60	0.55			3.83	2.17	1.29		4.00	7.33			3.89	5.27		
Negative	3.67	2.00			1.36	3.40			2.40	2.98			11.42	13.83			12.43	14.00			11.79	13.93		
Total involvement	4.78	2.00	1.30		1.55	4.60	1.59		3.00	3.18			15.25	16.00			16.43	21.33			15.68	19.20		
Dependency	0.89	0	1.73		0.18	1.60	2.06†		0.50	0.73			3.67	4.50			5.57	7.22			4.37	6.13	1.04	
(B) <i>Father</i> :																								
Positive	4.33	2.17	1.88†		3.00	3.80			3.60	2.91			8.92	6.83			6.00	3.44	1.88†		7.84	4.80	1.60	
Negative	3.89	2.33	1.21		1.45	3.40	1.35		2.55	2.82			7.08	8.22			1.71	8.22	2.34†		5.11	5.87		
Total involvement	8.22	4.50	1.88†		4.45	7.20	1.12		6.15	5.73			16.00	9.17	2.11†		7.71	11.67	1.19		12.95	10.67	1.19	
Positive-Negative	0.44	-0.17			1.55	0.40			0.05	0.09			1.83	4.50			4.29	-4.78	3.18*		2.74	-1.07		
Dependency	1.67	1.00			0.73	1.20			1.15	1.09			1.00	0.67			1.00	1.44			1.00	1.13		
(C) <i>Mother</i> :																								
Positive	4.00	5.17			3.45	7.00	1.59		3.70	6.00	1.96†		13.67	12.00			10.57	11.44			12.53	11.67		
Negative	1.44	2.17	1.49		3.64	3.40			2.65	2.73			2.83	0.67			0.86	1.33			2.11	1.07		
Total involvement	5.44	7.33			7.09	10.40	1.12		6.35	8.73	1.49		16.50	12.67	1.07		11.43	12.78			14.63	12.73		
Positive-Negative	2.56	3.00			-0.18	3.60	1.71		1.05	3.27	1.64		10.83	11.33			9.71	10.11			10.42	10.60		
Dependency	3.67	4.67	1.06		3.82	3.00			3.75	3.91			1.50	0.67	1.28		0.43	1.11			1.11	0.93		
(D) <i>Positive-Negative:</i> <i>Mother-Father</i>	2.11	3.17			-1.73	3.20	1.91†		0	3.18	1.84†		9.00	6.83	1.81†		5.43	14.89			7.68	11.67		
(E) <i>Self</i> :																								
Positive	2.11	6.50	2.08†		1.18	1.60			1.60	1.00			1.33	1.83			0.71	1.33			1.11	1.53		
Negative	1.00	0.50			1.27	1.40			1.15	0.91			2.17	1.17			0.43	0.89			1.53	1.00		
Total involvement	3.11	1.00	1.63		2.45	3.00			2.75	1.91			3.50	3.00			1.14	2.22			2.63	2.83		
Positive-Negative	1.11	0	1.80†		-0.09	0.20			0.45	0.09			-0.83	0.67	1.05		0.29	0.44			-0.42	0.53		
Dependency	0.89	0.33			1.09	1.40			1.00	0.82			5.25	2.67	1.97†		3.43	4.11			4.58	3.53	1.06	
(F) <i>Siblings</i> (all siblings):																								
Positive	6.25	7.50			7.82	4.75	1.38		7.16	6.40			15.92	14.17			12.57	11.22			14.68	12.40		
Negative	7.13	9.00	1.06		8.27	5.75			7.79	7.70			11.42	15.33			17.71	9.44			13.74	11.80		
Total involvement	13.38	16.50	1.39		16.09	10.50	1.15		14.95	14.10			27.33	29.50			30.29	20.67			28.42	24.20		
Positive-Negative	-0.88	-1.50			-0.45	-1.00			-0.63	-1.30			4.50	-1.17			-5.14	1.78			0.95	0.60		
Dependency	1.00	2.00	1.49		2.27	1.25			1.74	1.70			9.75	12.83			7.29	6.89			8.84	9.27		
(G) <i>Most Involved Siblings:</i> <i>Positive-Negative</i>	-1.38	-4.17	1.81†		-0.18	-2.00	1.01		-0.68	-3.30	2.08†		1.92	-5.17	1.21		-8.29	1.44	3.02*		-1.84	-1.20		
NUMBER OF CASES	9	6			11	5			20	11			12	6			7	9			19	15		

NOTE: The entries in this Table represent the mean scores for each group of subjects.

* .01 level (2-tailed) † .05 level (2-tailed) ‡ .10 level (2-tailed)
Only values of *t* equal to or greater than 1.00 are included in the Table.

to be negative ($\cdot 02$ level). A predominantly ambivalent relationship toward all siblings is expressed by younger children of good providers.

When the data for older and younger girls are combined, a different pattern emerges. Girls whose fathers are better providers attribute fewer positive items to Nobody ($\cdot 10$ level). They give the Father figure fewer negative items ($\cdot 02$ level), so that the net reaction to him is more positive ($\cdot 10$ level) and, as a result, their net preference is more likely to be for the Father figure over the Mother ($\cdot 10$ level). They show more total involvement with siblings ($\cdot 10$ level), and this holds for both positive items ($\cdot 05$ level) and negative items ($\cdot 02$ level).

(b) *Discussion.* The father's adequacy as a provider affects boys and girls differently. These differences hold true in both the older and younger groups.

Boys whose fathers are good providers are much more overtly involved with him, and also assign a large number of positive feelings to Nobody. While the assignment of negative feelings to Nobody may be considered as a sign of the repression of unacceptable feelings, the interpretation of positive feelings given to Nobody is less clear. It is suggested that for a male to express warm feelings toward another person is considered somewhat unmanly in our culture, and that the giving of these feelings to "Nobody" by boys whose fathers are more adequate providers may reflect a stronger identification with a masculine model.

The girls whose fathers are better providers show little hostility toward their father and he is often the preferred parent, but where the father is less adequate, much hostility is expressed toward him and the mother is preferred almost exclusively, particularly in the case of the older girls.

In these families the younger girls report more dependence on "Nobody" without the accompanying dependence on Self that would indicate self-reliance, suggesting that support is less available to them. This would seem to reflect a family situation in which the mother has had to take over and be the stronger figure. The daughters identify with her, but part of the effect of this identification is that they suppress some of their more feminine attributes, particularly the free expression of warm feelings and the open admission of dependency.

The father's adequacy as a provider also affects the pattern of sibling relationships; the nature of this effect varies for the different groups. The differences noted above in the sex of the sibling chosen can perhaps be understood by a closer examination of the particular siblings chosen. In families with more adequate fathers, the younger boys tend to be most involved with a sister who is slightly older, and to express both positive and negative feelings toward her, while the older boys are most involved with a younger brother toward whom they feel warmly. This parallels a normal Oedipal pattern, in which the younger boys express affection toward an older sister who may have, for them, some of the attributes of a mother figure, while the older boys, who have presumably established a firmer identification with their fathers, become strongly involved in a warm relationship with a younger brother, with whom they probably play a paternal or big-brother role.

When the father is less adequate, younger boys have as their strongest sibling relationship, a hostile one with a brother who may be older or younger, which may be a displacement of their low opinions of their fathers toward whom they express comparatively few feelings directly. The older boys in these families all have their strongest relationship with a much younger sister (six years younger, on the average); this relationship is either strongly positive or

negative, but not a mixture of the two. Such a pattern suggests a retreat from normal masculine relationships into passivity.

The girls with more adequate fathers express more feelings, both positive and negative, about siblings than do those with less adequate fathers. They are, in other words, more actively involved, emotionally, with other children in the family, while the girls with less adequate fathers suppress their warm feelings and direct their hostility toward their fathers. The younger girls with more adequate fathers are freer in the expression of their feelings toward siblings than are young girls whose fathers are less adequate, and they consistently express ambivalence, that is, both positive and negative feelings toward the same siblings.

In contrast, young girls with less adequate fathers express dislike (outgoing feelings) for siblings while they state that their siblings like them (incoming feelings). The non-reciprocal quality of this sibling relationship is further accentuated by the fact that they are most involved with a sibling who is on the average, six years older than themselves.

All but one of the older girls with more adequate fathers express the greatest involvement with an older brother (in several cases they are adults), and the feelings expressed are overwhelmingly hostile. It seems reasonable to assume that these brothers are father-substitutes, and that there is a reservoir of hostility toward their fathers that they cannot express directly, possibly because of his adequacy and the strength of his position in the family.

The father's adequacy as a provider appears to be an index of his more general adequacy in fulfilling the requirements of an adult masculine role. In families where the father fills this role, sex roles seem to be more clearly defined, so that children of both sexes show reactions appropriate to their sex at each age level. Where the father is inadequate and, one may assume, the mother takes over some of his functions, the boys seem to have a less solid masculine identification. They appear more passive, while the girls de-value their fathers and seem deficient in their capacity for emotional interaction.

SUMMARY AND CONCLUSIONS

Summary

Sixty-nine children in 28 families, 17 American Negroes, 46 Puerto Ricans, 6 Americans of European descent, were tested by the Bene-Anthony Family Relations Test. No attempt was made to distinguish between the various national groups, as these were all considered to be living under similar social conditions; that is, in the same metropolitan slum sub-culture.

The Bene-Anthony Test provides a paradigm of each child tested in terms of the child's feelings in regard to himself and to members of his family as these feelings are brought out in the test situation. Whether a different pattern of relationships can be discerned under special conditions of family life was the question asked by the writers of this paper. The comparison of the test scores achieved by the children as these were rated high or low on six qualitative variables in family life did bring out significant patterns in boys and girls of different age groups and in the group, as a whole.

Conclusions

1. The child who was rated as sick by the paediatrician and nurse was more involved with the parent of the opposite sex and more self-absorbed than his healthier counterpart.

2. In the families where the majority of its members had many episodes of illness the children expressed a marked preference for the mother tempered by feelings of lack of support and a tendency to withdraw from involvement with other children, a walling off each into his own seclusion.

3. In the situation of parents' inadequate marriage, no significant differences were brought out in the test scores of younger children. For the older children, however, when the marriage is less adequate the mother is preferred, and primarily positive feelings are expressed toward siblings. Also, there is strong expression of negative feelings toward the father by the girls but no change in feelings is expressed by the boys. A more balanced attitude towards both parents is demonstrated in the families where the marriage is more adequate, but there is likely to be intense dislike of one sibling coupled with warm feelings toward other siblings.

4. In 27 of the 28 families the observers felt that the mothers had considerable interest in their children; that there was only one woman who appeared to reject her progeny. The comparison of test scores with this particular variable brought out a pattern of identification by the older girls with the mother's role whenever the mother's interest was rated especially high.

5. The findings related to the variables concerning the father's interest were consistent with those described in 4 above in that the more interested fathers were better liked by their children and in those cases both parents share the children's positive feelings.

6. The father's ability to provide is the crucial variable in this study: when he is inadequate, much hostility is expressed toward him by the girls while the boys appear to displace this hostility toward a younger sibling of the same sex—and all children concentrate more on the mother. Positive identification with the father by the boys and a more ambivalent relationship with siblings prevails in families where the father is a better provider.

7. The test results reflect the true life situation as it appears in the society where these children live. A man is judged by his ability to provide and by the family's resulting standing among their neighbours. A father who is strong in this sense can serve as an adequate model for his sons, and enable his daughters to assume an appropriate female identification. It is also recognized that a man who is sick cannot work, so that identification patterns of boys and girls in "sick" families are less distorted than they are in families whose fathers are poor providers.

8. Ambivalence—a mixture of positive and negative feelings towards parents and siblings is expressed more freely in those families where the parents are more interested in the children, the marriage is more adequate, and the father is a better provider. In the test situation, as in a life situation, the expression of ambivalence may be an index of a healthier emotional atmosphere.

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THERAPEUTIC VALUE OF THIOPROPERAZINE AND THE IMPORTANCE OF THE ASSOCIATED NEUROLOGICAL DISTURBANCES

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CLINICAL trials of thioproperazine (7843 R.P.; "Majeptil") 2-dimethylsulphamoyl-10-(3-4'-methyl-1'-piperazinypropyl) phenothiazine methane-sulphonate, carried out in France by Delay, Deniker *et al.* (1959b); Perrin, Lambert *et al.* (1958); Coirault *et al.* (1959); and in America by Denber *et al.* (1959, 1960), have shown that it is a highly effective agent in the treatment of schizophrenia and acute mania. To examine the claims made for the drug's value in deteriorated or vegetative schizophrenics, and in other cases that have resisted chemotherapy, a trial was undertaken in this country.

A difference of views as to whether the neurological phenomena evoked by the drug were therapeutically advantageous or not existed between the original investigators; Delay, Deniker *et al.* (1959b) postulated a definite correlation between therapeutic effect and neurological disturbances, whilst Perrin, Lambert *et al.*, believed there was no such relation. Our observations lend support to the former hypothesis and also draw still closer the parallel between the drug-induced symptoms and those of epidemic encephalitis, as observed by Delay, Deniker *et al.* (1959a).

The conduct and results of this trial will be described in three parts: the first dealing with the psychiatric aspect; the second with the neurological phenomena; whilst the third proposes possible explanations as to why the neurological manifestations should be correlated with therapeutic value in schizophrenia.

CHEMICAL AND PHARMACOLOGICAL CHARACTERISTICS

Thiopropazine is a phenothiazine derivative which differs from chlorpropazine only in that the chlorine atom has been replaced by a dimethylsulphamoyl group.

The pharmacological properties of the drug have been fully described by Courvoisier *et al.* (1958), and it is worthy of note that its anti-emetic action, as measured by the anti-apomorphine tests in dogs, is 150 times more powerful than that of chlorpromazine. Yet more interesting, perhaps, in view of the clinical findings, is its ability to produce akinesia and catalepsy in the rat at a dose of 0.5-1 mg./kg., an action 150 times greater than that of chlorpromazine.

PART I: PSYCHIATRIC ASPECT

METHOD

The high therapeutic potency of the agent, coupled with the neurological phenomena so frequently produced by it, ruled out any worthwhile comparison with a placebo or a less active compound. As the majority of the patients were selected because of the chronicity and resistant nature of their disorders, they were able to act as their own controls.

Before starting the treatment, all other medication was suspended for a period of at least 4 weeks. In a majority of the patients, Delay's "discontinuous treatment" was employed. Initial dosage was 5 mg., orally, t.d.s., which was increased daily by 5 mg. t.d.s. until a maximum degree of muscular hypertonus was induced. This optimal dosage was then maintained for 5 days; the treatment was then interrupted. After a few days, muscle tone returned to normal, and maximum psychiatric improvement could be observed.

Further courses were considered necessary where psychiatric response was incomplete. In such cases, the patient received the optimal dosage discovered in the first course from the outset of the subsequent course or courses, this level being maintained for 5 days. If psychiatric response to the first course was adequate, however, maintenance treatment with doses of 1-10 mg. daily was instituted after a few days.

The average number of courses required was three, and the optimal dosage varied from 15-90 mg., orally, t.d.s. The intramuscular route was used only in 3 patients for whom oral administration was inconvenient; this was continued for 2 or 3 days until the drug could be given orally. A correlation between dosage and body-weight, as suggested by Denber, was not found with our patients, but it was observed that those under 25 years of age, of either sex, required less of the drug than older patients.

Seven patients received continuous treatment with slowly increasing dosage, from 5-25 mg. t.d.s., for several weeks. Optimal dosage was considered to have been reached when mental improvement became marked. In these cases, neurological disturbances were largely avoided either by reducing dosage on their appearance or by combating them with anti-parkinsonism agents.

CLINICAL MATERIAL

During eleven months, 60 patients were treated, 42 of whom were male and 18 female. With the exception of 2 manic-depressives, all the patients were schizophrenics with an average duration of illness of 10 years. Most of the patients were English-speaking, but there was a small number of Poles whose serious language difficulties had a deleterious effect on the ultimate success of the treatment.

All the patients had previously received some form of physical treatment and one or more neuroleptic agents with little or no benefit. Some presented with florid symptoms, whilst others were largely vegetative and displayed various stages of "schizophrenic deterioration".

RESULTS

Thirty-two of the 58 schizophrenic patients achieved total remission of their symptoms. Ten were very much improved in that they have lost most of their schizophrenic symptoms and are thus enabled to lead an active and useful part in the hospital. Fifteen were improved in so far that they no longer present any

nursing problems, being able to care for most of their needs despite the retention of some of their psychotic symptoms. One patient was a total failure. The two manic patients responded adequately.

TABLE I
Table of Results
Females

		No. of Patients	Average Duration of Illness	Remission of Symptoms	Results		
					Very Much Improved	Improved	Failed
Hebephrenic		4	4 years	1	0	3	0
Paranoid ..		5	5 years	1	0	4	0
Simple ..		3	3½ years	2	0	1	0
Vegetative ..		4	14 years	0	3	1	0
Catatonic ..		0	0	0	0	0	0
Total ..		16	6½ years	4	3	9	0

Males

Hebephrenic	13	7 years	9	2	2	0
Paranoid ..	9	3½ years	6	1	1	1
Simple ..	3	11 years	2	1	0	0
Vegetative ..	16	15 years	11	3	2	0
Catatonic ..	1	12 years	0	0	1	0
Total ..	42	10 years	28	7	6	1

The above table reveals that results amongst male patients were superior to those in the females. Two possible explanations can be advanced for this. Firstly, a majority of the females received prolonged, uninterrupted treatment; secondly, 6 of the females had previously been leucotomized. That previous leucotomy may be related to subsequent poor results with drug-treatment has been noted by McDonald (1959). In this respect, it is notable that the patient who failed completely was the only leucotomized male. In none of these 7 patients was any muscular hypertonus observed.

Seven male and 2 female patients have been discharged. Both of the females and 4 of the males are receiving small maintenance doses and attend a follow-up clinic regularly. They have remained well for many months and made satisfactory social adjustments. Three male patients discharged themselves and are receiving no maintenance treatment, but follow-up visits have revealed no signs of relapse. Of the remaining patients in the first category, 5 are receiving rehabilitation training prior to discharge, whilst the residue will be discharged when suitable arrangements can be made for them.

SIGNS OF PROGNOSTIC VALUE DURING TREATMENT

Although no indications as to the ultimate outcome of the treatment were found to be of aid in selection of patients, within a short time of its commencement certain somatic and psychological signs appeared which often presaged a favourable result. In the psychiatric sphere, early, though temporary, mental improvement; the appearance of florid symptoms in withdrawn patients; and

mood swings between depression and euphoria, frequently indicated a favourable outcome. Extracts from case reports may serve to illustrate these points:

1. *Early Mental Improvement*

B., aet. 46. Wood-carver.

This patient had been suffering from schizophrenia for 15 years. He was mute, solitary, inaccessible, disorientated, had no memory for past events and was occasionally impulsive and aggressive, none of which symptoms had been alleviated by electroplexy, chlorpromazine, pecazine, or trifluoperazine. Three days after starting thioproperazine he requested a newspaper which he read with interest for the first time since admission. Three courses of treatment, covering a period of 35 days, were required to produce remission in this patient. On a maintenance dose of 2 mg. daily he has remained well for 10 months.

2. *Appearance of Florid Symptoms in a Vegetative Case*

G., aet. 44. Polish soldier.

On admission, 16 years ago, this schizophrenic patient was hallucinated, over-active and aggressive; but subsequently he had become mute, inactive, withdrawn, inaccessible, slovenly and unkempt. This deteriorated state, which had persisted for many years, was in no way influenced by electroplexy, chlorpromazine, or any other measure. On the first day of treatment with thioproperazine, after the second 5 mg. dose, he became restless, talkative, and aggressive. Echopraxia and echolalia, in Polish, German, or English, were marked. On the second day he was calm and more responsive; and on the third he showed interest in his surroundings, and his customary attitude of suspicious hostility was replaced by one of notable amiability; whilst on the fourth day his memory for events prior to his illness returned. During the first interruption he displayed an erratic desire to work. He occasionally scrubbed the floor, prised up floorboards, and dismantled his bed. For a time this incessant wish to work, which continued night and day, disturbed the ward so much that the patient had to be sedated. During subsequent courses, improvement continued and his behaviour became more normal. He is now employed on the farm where he works well. Although not particularly sociable, he is co-operative and friendly, and keeps himself clean and tidy.

3. *Mood-swings*

S., aet. 37. Tailor.

This patient had been suffering from schizophrenia for 15 years. He was deluded, vividly hallucinated, disorientated, slovenly, unemployable, and unable to give any coherent history. Electroplexy, chlorpromazine, and prochlorperazine had failed to promote any significant improvement. On the third day of treatment with thioproperazine, his hallucinations disappeared. On the fourth day he became euphoric, but was alert and well in touch. This state persisted into the fifth day when it was suddenly replaced by one of marked depression with ideas of unworthiness which lasted for several days after interruption of treatment. A further brief period of euphoria then occurred and was rapidly followed by complete remission of all psychotic symptoms. On a maintenance dose of 5 mg. daily, the patient has remained symptom-free for 8 months.

Hallucinations yielded readily and rapidly to the treatment. Thirty-six of the 40 hallucinated patients lost this symptom. In the great majority, the hallucinations disappeared completely within a few days of starting treatment, whilst in a few there was attenuation of the disturbance for several days prior to eradication.

Behaviour disturbances, when actuated by hallucinations, resolved themselves coincidently. Such disturbances, when lacking this association, usually disappeared within 24 hours of starting the treatment. Contrarily, with the withdrawn, vegetative patients, the treatment commonly awakened florid symptoms which induced behaviour disturbances of a transitory nature.

Apathy, as displayed to a considerable degree by 17 of the patients, was usually lost in the latter part of the preliminary course. Frequently the first sign of this change in such a patient who, perhaps, had never been known to assist in any task before, was a sudden desire to carry out some type of work. The first efforts were erratic and poorly sustained, but they were purposeful and

repeated as often as possible. But as they usually coincided with the development of maximum muscular hypertonicity, the patients found it physically impossible to continue with their attempts. When the drug was withdrawn and the hypertonicity had dispersed, however, the desire to work returned more strongly and with a steadily increasing ability to concentrate. Concurrently with this altered behaviour we observed, in a majority of these patients, a return of personal pride, an improved attitude to the staff, and a tendency to consort with their fellow-patients.

Delusions, when unsystematized or actuated by hallucinations, dissipated rapidly, the patient readily admitting that his distorted ideas were due to his mental illness. More complicated delusions, particularly those of a paranoid or phobic nature, were not so readily dispelled. For patients so afflicted, we used psychotherapy which we found particularly effective because of the notably increased suggestibility of those under treatment with thioproperazine.

SUGGESTIBILITY

Enhancement of suggestibility was observed from the earliest days of the treatment. Revealing itself firstly in the form of unusual obedience in previously resistive or negativistic patients, as the course advanced, and particularly during the interruption, when the patient's mental state was sufficiently improved to benefit from psychotherapy, this heightened suggestibility proved very valuable. The following case-history helps to illustrate this point:

R., aet. 31. Leather-cutter

This patient, during his five years of schizophrenia, had received insulin coma therapy, E.C.T., chlorpromazine, prochlorperazine, trifluoperazine, methylphenidate, and imipramine without notable effect. He was hallucinated, tense, agitated, depressed and possessed of a fixed delusion concerning an obscure murder, a vivid account of which had been engraved on the patient's mind by his grandmother when he was 11 years of age.

Soon after starting thioproperazine treatment, he had two excitomotor attacks. The first of these was terminated, after 30 minutes, by 2 mg. benztropine. The second occurred some 4 hours later, and, as he was found to be highly suggestible, light suggestion was tried instead of an anti-parkinsonism agent. This proved very successful, for not only was the attack stopped within five minutes but he never suffered from such attacks again. On the following day his hallucinations disappeared but the delusion remained.

On the first day of the interruption he was agitated but unusually willing to describe and discuss his morbid fears. Suggestion was again used, and on the following day the patient showed a remarkable change. He was bright and cheerful, and had dismissed his delusion as being "childish rubbish". Within 20 days of starting treatment, the patient appeared to be in normal health. He has remained well on 2 mg. thioproperazine daily for 5 months and is soon to be discharged.

Psychotherapy, facilitated by this enhanced suggestibility, was employed successfully in a majority of cases. Unfortunately, the 5 male Polish patients could not be assisted to any extent by such measures. Displaying as satisfactory an initial improvement as the other patients, these war-veterans progressed less quickly and showed a greater tendency to relapse. Language difficulties could never be overcome completely, particularly as interpreters were regarded with even greater suspicion than was commonly displayed towards the doctors and nurses. The same attitude of suspicion was directed towards their compatriots, with the result that, although 4 of the 5 patients are now usefully employed in the hospital grounds, they remain solitary and friendless. It is possible that this attitude and the partial nature of the response may be due to their war-time experiences and to the alien circumstances in which they find themselves. Different reactions of different ethnic groups to psychotropic drugs has been observed by others (W.H.O., 1958) and are accordant with these findings.

AFFECTIVE DISORDERS

Thiopropazine was also used in the treatment of acute mania. In these cases a rapid response to the drug was observed and satisfactory therapeutic improvement obtained within a few hours of starting treatment. The initial dosage of 15 mg. t.d.s. was given by the intramuscular route, but 5 mg. t.d.s., orally, was found adequate for subsequent treatment. Discontinuous treatment was not employed on these patients who have retained a satisfactory equilibrium on a maintenance dosage of 10 mg. daily.

COMPLICATIONS

Three cases of hypostatic-type pneumonia occurred during the trial. The patients were males, and were all young and physically normal. In each instance the complication appeared during a phase of akinesia produced by the drug, and seemed to be due to lack of any effort to cough or expectorate, combined with an increased mucous secretion. Response to broad-spectrum antibiotics was rapid and adequate, but we feel that this complication would not have arisen had we had more experience with thiopropazine. Later in the trial, any patient developing very marked akinesia was observed closely and subjected to physiotherapy by the nurses, with the result that we had no further trouble of this nature.

Seven of the male patients became incontinent during preliminary courses of treatment. This seldom lasted more than a few days and was not repeated during subsequent courses. Contrarily, 2 patients who were incontinent prior to treatment, after an initial worsening of the symptom, regained and retained bladder control for the first time for many years.

Transitory retention occurred in 2 patients. Neither complained of the condition nor did they experience any discomfort when the distended bladders were palpated. The oral administration of benztropine (2 mg.) relieved the condition within 30 minutes and there was no repeat.

Herpes labialis was seen in 5 patients; conjunctivitis in 4; and 1 patient developed a tongue infection following biting the organ during an excitomotor attack.

Headache occurred in 4 patients. In one the pain was occipital, but in the others it was in the frontal region and unilateral.

INVESTIGATIONS

Routine examinations of the blood revealed no abnormality. Liver-function tests were equally negative. Hypotension did not occur in any of the patients.

PART II. SIGNS AND SYMPTOMS EVOKED BY
THIOPROPAZINE

DURING the period of discontinuous treatment with thiopropazine, many diverse neurological signs and symptoms may be encountered. They resemble closely those seen in epidemic encephalitis, and there is a similar tendency for them to fall into recognizable groups or syndromes with somewhat broad chronological demarcations. Thus can be discerned an akinetic state, an akineto-hypertonic state, and an hyperkineto-hypertonic state. Concomitantly with all these states may be seen disturbances of autonomic function, chiefly

affecting the production of sweat, sebum, and saliva. Finally, excitomotor disturbances are sometimes seen.

THE AKINETIC STATE

Within 4 to 24 hours of receiving the drug the patient shows a marked decline in kinetic activity. He sits or lies motionless with his eyelids lowered, although there is no true ptosis. The appearance is that of extreme lethargy, and, indeed, some patients fall into a real sleep. With these latter, there is a tendency towards an inversion of the sleep rhythm, the patients becoming more active and alert at night. Whether the patient is in a state of true or simulated sleep, he can be awakened with remarkable ease. To address him is sufficient to bring him to immediate consciousness, the normal interim waking period being entirely absent.

The patient's face is pallid, particularly in the circumoral region, and there is a notable lack of expression save in the eyes which appear to possess an unnatural brightness. Despite the apparent stupid apathy, questioning may reveal the patient to be much more alert and in touch than he was before treatment. After a short while, however, answers are not given so readily, and those extracted with difficulty from him may show marked economy of expression. When told to smile, or show his teeth, the command is obeyed, but, apart from frequent episodes of yawning, there is no spontaneous change in the facial expression.

During this early stage of the treatment it is common for hallucinations to disappear, but although the patient may have been afflicted with them for many years and will now admit not only their existence but their sudden eradication, he rarely displays any interest in the matter. In reply to questions about his health, he may state that he does not feel well without elaborating further; or he may admit to pains and stiffness in his joints, but betrays no concern with these complaints.

Physical examination reveals a similar want of volition and spontaneity. There is no lack of co-operation, even patients whose usual attitude was hostile and aggressive becoming passively obedient to command, but there are no spontaneous movements and there is economy of action, which becomes more marked as the examination proceeds. Furthermore, there is bradykinesia, which in some cases is so pronounced that the patient may take over a minute in rising from the supine to the sitting position, having to be prompted several times before the movement is completed. This bradykinesia seems to be entirely due to volitional inertia, as there is no apparent physical cause at this stage, and support is lent to this view by the marked differences in response between voluntary and reflex behaviour, notably in the lower limbs. The plantar teguments are hypersensitive, sometimes so markedly that mere brushing of the sole of one foot leads to true defensive withdrawal of both legs; yet the patient appears to be incapable of moving his legs on request, and able to make only very slow, hesitant movements on command. There is no increase of muscular tonus and no inco-ordination of movements, but disturbances of tendon reflexes may be evident very early in treatment. So soon as the examination is over, the patient relapses into his somnolent state or resumes his interrupted sleep.

Autonomic disturbances occur very early in treatment. Sweating of a moderate to severe degree is an almost constant feature and may begin within a few hours of the first dose of the drug. Seborrhoea is almost as common, and appears within 12 hours of commencement. Most prolific on the face and

scalp, it lends to the immobile facies a glistening sheen well in keeping with the wax-like countenance. Increased salivation is very uncommon during the akinetic stage.

THE AKINETO-HYPERTONIC STATE

After the patient has been in the akinetic state for some 12 to 48 hours, a parkinsonism-like condition develops. There is a gradual or rapid increase of muscular tonus in certain parts of the body. The lower limbs are most commonly involved, the upper limbs less often, whilst the muscles of the head and neck are affected least. Before the onset of frank hypertonia fasciculations of the tongue are commonly seen, and there may be other transient neuromuscular disturbances. A fine tremor of the fingers is also very common.

The appearance of the patient at this stage differs little from that described in the akinetic state. He is no longer drowsy, but lies inert, making no spontaneous movement. The face is a little more mask-like, the seborrhoea and sweating more pronounced, and sialorrhoea, sometimes of remarkable intensity, may be present. Questioning reveals a higher degree of alertness and the attention is sustained more readily, the patient tiring less quickly. Although the same lack of volition and spontaneity is maintained, the emotional state may be notably different: euphoria, quite out of keeping with the patient's appearance and physical state, is occasionally seen, but more commonly he is depressed to a mild or moderate degree and may express self-accusatory ideas.

Physical examination shows hypertonia of various types and varied distribution as well as diverse reflex peculiarities. Bradykinesia is very marked, the pre-existing poverty of volition combining with the mechanical difficulties caused by the hypertonia to produce very slow and badly co-ordinated movements.

THE HYPERKINETO-HYPERTONIC STATE

The most notable factor differentiating this state from those preceding it is the presence of motor restlessness. From a state of complete inertia there arises one in which there is a desire for incessant activity. Although the muscular hypertonia is, if anything, more pronounced than that seen in the second state, thus making movement very difficult, the patient is compelled to move. He cannot sit or stand inactive. He must walk about constantly but will not be satisfied with one part of the ward, ever seeking a change of action and of locality. It is at this stage that he may endeavour to work, but, as with all his other activities, any attempt at one particular task is soon superseded by the desire to try something different. Questioned as to his behaviour, the patient may say that only by constant walking can he allay his restless feelings, or that "something pushes him on". The predominating mood is depression, but there may be mood-swings, short periods of euphoria interrupting the former, particularly in the evening. When this akathisis condition is marked, insomnia may be present but is not a common cause for complaint.

When treatment is interrupted, which is done after maximum muscular hypertonia has been present for 5 days, all the drug-induced symptoms disappear without sequelae within a few days.

The above descriptions of the three main states are based on observation and daily examination of the 42 male patients in the trial, but it must be

emphasized that they indicate only a general pattern of behaviour. The drug-induced phenomena may vary quantitatively and qualitatively not only from one patient to another but in the same individual during different courses of the treatment. Thus it is necessary to describe the phenomena separately.

1. NEUROLOGICAL DISTURBANCES

A. *Affection of the motor system*

(i) *Disturbances of muscular tonus*

Of the 42 male patients receiving the treatment only one failed to develop some degree of muscular hypertonus. The commonest time for the first appearance of this hypertonia lay between the third and fourth days of treatment in the preliminary courses, after a total of between 60 mg.-90 mg. of the drug had been ingested. In 6 patients, however, the phenomenon did not appear until the second course of treatment, but 4 of these had received anti-parkinsonism drugs during the initial course.

The degree and extent of hypertonia was variable. All modifications from fine cogwheel rigidity confined to one limb to gross hypertonia involving all the limbs and many of the muscles of the head and neck were seen, and it was not uncommon to find varying degrees in different parts of one patient at the same time. The lower limbs were far more frequently involved than the upper, and to a greater degree, whilst the head and neck muscles were affected in only 6 of the cases. Hemihypertonia was observed in 18 patients at some stage of treatment with involvement of the right upper and lower limbs in 13 of this total; whilst contralateral hypertonia was seen in 11 patients, 6 of whom had involvement of the left upper and right lower limbs: in all these cases muscular tonus in other parts of the body was apparently normal. Transitory involvement of isolated muscle groups, notably the rectus femoris and vastus lateralis, was seen occasionally.

Cogwheel rigidity, varying from very fine to coarse, was more commonly encountered in the arms and was analogous to that seen in post-encephalitic parkinsonism. The more usually observed hypertonia, however, was of a more particular kind. In its mildest form this showed itself as a slight but sensible resistance to passive movement, becoming more marked as full extension or flexion was reached. If the forearm when being passively extended was released before full extension, there would be a temporary rebound for a few inches before completing the fall to full extension. Rapid passive movements of the limb abolished hypertonus of this mild degree, but slowly carried out movements accentuated it. When gross hypertonia was present, all the above phenomena were exaggerated or modified. Resistance to passive movement was very considerable, particularly in the legs, and if the actions were repeated several times the limb became rigid. Rapid movement was impossible unless the patient's attention was distracted; then, momentarily, the movement would be much easier, but immediately attention was restored, the resistance offered by agonists and antagonists would be sufficient to arrest all movement. In place of the rebound phenomenon, there was a tendency towards fixation of attitude, the limb, if released, remaining static for some seconds before descending very slowly to the bed.

Spontaneous movements, except abnormal ones, were not observed in markedly or grossly hypertonic limbs, nor would light persuasion induce any movement. Stern command, however, would, in many instances, lead to jerky, badly co-ordinated, and severely bradykinetic obedience, but such

efforts were ill-sustained and rarely repeated. Nevertheless, even patients with apparently rigid limbs were able to rise from their beds unaided if it was essential for them to do so.

Hypertonia of the head and neck chiefly affected the sternocleidomastoid, the upper portions of the trapezius, and the masticatory muscles, either individually or conjointly. Thus, with the first groups various attitudes of extension and tilting of the head and neck were seen. Involvement of the masticatory group was sufficiently pronounced in 2 patients to prevent eating, and the drug was withdrawn temporarily with rapid loss of the hypertonia.

Preceding, accompanying, and sometimes succeeding the hypertonia, various abnormal muscular movements have been observed:

Fasciculations were observed in 14 patients particularly affecting the tongue, the biceps, and the quadriceps. In the tongue, these movements were often the first signs of the development of hypertonia and appeared very early in treatment, later they were replaced by or masked by other phenomena such as "trombone" movements. In the brachial biceps and quadriceps they commonly presaged the appearance of myoclonic movements.

Myokymias, although less common, appeared synchronously, and affected small portions of the superficial abdominal and thoracic musculature.

Myoclonus was common during the hypertonic period. With a rhythm varying between 80-120 per minute, it chiefly affected the quadriceps and brachial biceps. Augmented by emotion and cold, and diminished by alterations of attitude, the condition was rarely under voluntary control. Physical restraint, either by the patient or the examiner, led to temporary arrest, but the slightest tap on the affected area was sufficient to set it in motion again. It was always abolished by sleep.

Tremors of varying type were seen in 27 cases. The earliest and commonest variety was a fine tremor of the fingers. With the onset of hypertonia, coarser tremors of greater amplitude were seen in the arms, but the fine, finger tremors remained discrete from these. Augmented by cold and emotion, they were abolished temporarily by movements of intention and by command.

Choreiform movements were seen in 19 patients. The earliest to appear were those affecting the mouth, curious chewing movements with clucking of the lips and tongue replacing the mouth-gaping of the akinetic phase and persisting throughout the two hypertonic stages. Movements of the feet, resembling a dilatory form of marking time, occurred in all the patients who displayed akathisia but, although forming a part of that syndrome, tended to remain for several days after the desire to walk about had passed. Isolated choreiform movements of fingers and toes were seen in 7 patients, but large joints, such as shoulders and hips were but rarely implicated. In only 2 patients were the movements complicated and rhythmical. In one of these, the cycle began with gaping of the mouth which was followed by raising the left shoulder, with a simultaneous craning of the neck to the right, then a slight bowing of the trunk rapidly succeeded by raising the legs alternately and rapidly some 18 inches from the ground, the whole cycle occupying about 5 seconds and being repeated in the same order almost at once. The other patient displayed the condition spoken of as saluting chorea. All such movements could be stopped temporarily by command and disappeared during sleep.

Athetotic movements were chiefly confined to the tongue, in the early stages of the akineto-hypertonic state, and to the fingers and toes during excitomotor attacks.

(ii) Reflexes

Modifications of the tendon reflexes were seen in all the patients. Accompanying the akinetic symptoms, they were precocious signs of the drug's activity. Often within a few hours of the first dose, diverse alterations were seen which included exaggeration in all limbs, in arms or legs alone, unilaterally, contralaterally, or confined to one member. As treatment continued, individual variability from day to day or even from hour to hour was remarkable, it not being uncommon to find all the above-mentioned modifications in one patient at different times during a 24-hour period. Furthermore, temporary diminution or absence of tendon reflexes, generalized or localized, occurred in 13 cases, and in 2 patients in whom one or more reflexes could not be elicited prior to treatment, the response became brisk whilst they were receiving the drug.

Bilateral patellar clonus was seen in 3 patients and unilateral in 2; whilst ankle clonus was found bilaterally in 3 and unilaterally in 4 patients.

Extensor plantar responses were seen in 14 patients, but of this number, the phenomenon was bilateral in only 3. Often occurring on the third or fourth day of treatment, it rarely persisted for more than two days. In 4 of our cases the manifestation was seen first on one side, then, when that had become normal, on the other. There appeared to be little connection between this phenomenon and any other neurological peculiarity.

Although exaggeration of the tendon reflexes, particularly the patellae, frequently coincided with muscular hypertonicity, this was not always the case. Sometimes the reverse applied in either direction, and occasionally unexpected phenomena occurred such as tonic contraction of the right vastus internus muscle when the left patella reflex was elicited, or a biceps contraction appearing when the supinator was being sought. Cremasteric, masseteric, abdominal, and epigastric reflexes were equally diverse and unpredictable.

(iii) Disturbances of muscular co-ordination

During the akineto-hypertonic stage, 10 patients showed mild to moderate dysidiadochokinesis; 3 had transitory ataxia, and in one of these Rombergism was pronounced.

(iv) Disturbances of volition and power

Akinesia and bradykinesia have already been described, but we wish to repeat that both appear to be symptoms of volitional disturbance affecting all parts rather than of muscular power. In 3 cases, however, there was true diminution of power affecting the right arm and hand in each instance and lasting for two days.

(v) Catalepsy and disturbances of locomotion

The adoption of strange attitudes was seen in 10 patients. Lasting for some 2 to 10 minutes, these included: lying on one side with both arms held out and demi-flexed; lying with trunk flexed and arms folded round the legs; lying with both legs held above the head; crouching and praying attitudes; and lying with the trunk on the bed and the head touching the floor, the arms flexed, wrists abducted, and fingers extended. Only one patient was able to describe his feelings during such an episode. He said that he was unable to move his limbs in any direction he desired, yet they would take up positions against his will and he was powerless to stop them. He experienced no

sensation of fatigue even when a limb was held in an unnatural position for 10 minutes, but he was distressed by the conflict between will and action, fearing that he might be permanently paralysed.

Akathisia affected 20 patients and was confined to the hyperkineto-hypertonic phase. In some cases the movements were automaton-like and imitated exactly by other patients receiving the treatment.

(vi) *Ocular disturbances*

Dilatation of the pupils was seen in 3 patients and contraction in 4. The Argyll Robertson phenomenon occurred in 3 cases and in 1 a reversed reaction was seen. Two patients complained of transient blurring of vision and 2 others of difficulty with accommodation. Nystagmus was observed in 3 patients. Examination of the fundi revealed no abnormalities.

No true ptosis was seen, but 4 patients, during the kinetic stage, displayed trembling of the lowered lids which disappeared when they were ordered to open their eyes. Rapid blinking of the lids was seen in 7 patients. An unnatural brightness of the eyes, like that sometimes seen in phthisis, was observed in 14 patients.

B. *Affection of the sensory system*

Apart from marked hypersensitivity of the plantar teguments, which was seen in 14 patients, sensory disturbances were not common. Anaesthesia, of the glove and stocking type, occurred in 4 patients. In 3 of these the right hand and a varying area of the right arm were affected, whilst in the other the right foot and part of the right leg were involved as well as the right hand. Coincidentally there was loss of kinaesthetic sense in 2 of these patients, involving ankles and toes bilaterally in one and the right fingers and toes in the other; in 1 there was delayed conduction time in the left hand; in 2 there was diminished pain sense in the achilles tendons. These 4 patients, and 2 others, also displayed loss of vibration sense involving both ankles in 2, the left wrist in 2, the right arm and leg in 1, and the left elbow and wrist and right ankle and patella in the remaining patient.

None of these disturbances lasted for more than 3 to 4 days.

C. *Affection of the autonomic system*

The commonest disturbance in this field was sweating, only one of the 42 patients in the series failing to show any increase throughout treatment. Commencing within a few hours of the first dose, this symptom continued throughout the course, or courses. In some cases the palms and soles were most notably affected but in the majority the condition was generalized. In addition to the constant hypersecretion, a number of patients showed "attacks" of sudorrhoea lasting 30-60 minutes, during which time the bed-clothes had to be changed several times. Because of this continuous extra-renal fluid loss we greatly increased the daily fluid intake, but even when this was pushed to the limit, the discrepancy between intake and output sometimes exceeded 30 oz. Because of this policy of replacement, we saw none of the oliguric symptoms reported by the French workers.

Seborrhoea was seen in 32 of the patients. Occurring some hours later than sweating, it was largely confined to the face and scalp and was sometimes of such severity that the face glistened and the hair appeared to have been dressed with grease.

Sialorrhoea occurred in 24 patients. Rare in the akinetic state, it appeared spasmodically at unrelated periods during the hypertonic stages, taking the form of "attacks" lasting several hours during which the quantity of saliva secreted was remarkable.

Lachrymation occurred bilaterally in 2 patients and unilaterally in 1 other.

Bradycardia was observed in one patient (the failure), and tachycardia, apart from that accompanying excitomotor attacks, occurred in 2 patients, lasting less than 2 hours in each. In no case was there any significant alteration in blood-pressure.

Retention of urine occurred in 2 patients. The condition was discovered during examination and, despite the considerable bladder distension, neither complained nor was any discomfort felt from palpation. Benztropine, 2 mg. orally, relieved the condition within half an hour and there was no recurrence. Five patients displayed temporary incontinence of urine during the akinetic stage, but 2 others who before treatment were doubly incontinent, acquired bladder and bowel control which was maintained.

Pallor of the face was seen in 8 patients and transient flushing in 2. In 2 other patients a marked difference in temperature from one leg to the other was discovered. The only catatonic patient lost the pre-existing cyanosis in his face and extremities on the second day of treatment.

D. Trophic disturbances

Erythematous plaques were seen on the face in 1 patient and on the anterior aspects of the ankles and lower parts of the legs in 2 others. In these latter, the condition was followed by swelling of the ankles with warmth and diffuse erythema but no pain or limitation of movement. The condition lasted for 4 days, as did the unilateral ankle oedema seen in 3 further patients.

E. Joint pains

During the akinetic stage, 15 patients suffered pain in various joints. The knees and ankles were most commonly involved, but other sites included fingers, wrists, elbows, and the sacroiliac joints. The pain was made worse by movement and, indeed, was usually discovered on examination by observation of the patient's expression, verbal complaint being rare owing to the akinesia; for the same reason, the characteristics of the pain were never discovered.

F. Excitomotor disturbances

Excitomotor attacks similar to those seen with other phenothiazine derivatives were seen in 8 patients. The attacks consisted of oculogyric crises, tongue-protrusion, trismus, opisthotonos, generalized muscular rigidity, restlessness, sweating, and tachycardia. Only one patient showed all these signs, the others displaying only a few. Duration of the attacks, if untreated, was from 10 minutes to 3 hours, but we preferred to terminate them by using one or other of the methods that will be described later.

In every instance the condition was seen during the first few days of treatment at relatively low dosage levels and was never seen during the hypertonic stages. A notable feature was the "contagious" nature of the syndrome. Five out of the 6 patients in one group, and 2 out of 4 in another were affected, whilst only one patient suffered a transient attack independently. All the patients were under 30 years of age, but they differed widely in weight and build.

Two other patients showed disturbances of respiration during the early stages of treatment. In one of these the attack consisted of tachypnoea followed by a period of stertorous breathing; in the other there was breath-holding followed by an irregular respiratory action reminiscent of Cheyne-Stokes breathing. These episodes lasted less than an hour in each patient and did not recur.

Correlation of neurological disturbances with psychiatric improvement

The results of this study lend support to the contention of Delay, Deniker *et al.* (1959b), disputed by Perrin, Lambert *et al.* (1958), and Denber *et al.* (1959, 1960), that the production of neurological disturbances by thioproperazine are of therapeutic value in schizophrenia. Furthermore, we believe that, of the many drug-induced symptoms outlined above, the most important is the muscular hypertonus. Our results indicate that the degree and extent of this condition can be correlated to the degree of psychiatric improvement.

Of the 28 male patients who underwent remission of their psychotic symptoms, 25 displayed gross hypertonia of more than one part of the body; 2 showed marked hypertonia of more than one part; whilst 1 had mild hypertonia in all limbs. Of the 7 patients who were very much improved, 3 displayed gross hypertonia in more than one part; marked hypertonia occurred in the other 4. Of the 6 patients who were improved, none displayed gross hypertonia; one showed marked hypertonia in more than one limb; 2 had mild hypertonia in more than one part; whilst in the remainder mild hypertonia was confined to one limb. The one failure displayed no hypertonia at any stage of his three courses of treatment.

Two patients who failed to display any hypertonia or any mental improvement in the first course of treatment, produced gross hypertonia in the second, after which they lost their psychotic symptoms; and a high proportion of those who eventually remitted after displaying gross hypertonia had shown only mild or moderate hypertonia and inadequate mental improvement in the first course. In those who showed only limited improvement, all save one displayed the same degree of mild hypertonia in every course despite increased dosage.

Because of the appearance of generalized excitomotor attacks which we regarded as undesirable, 4 patients received prophylactic benztropine (2 mg. orally t.d.s.) throughout the first course of treatment. This was successful in preventing such attacks but hypertonia was also prevented, and no mental improvement was seen in that course. In subsequent courses, in which excitomotor attacks were combated with paraldehyde, mild hypertonia followed by moderate mental improvement was seen in 2 of these patients, and the other 2 showed remission of symptoms after producing gross hypertonia.

Apart from hypertonia, there did not appear to be any significant relationship between the protean symptoms caused by the drug and therapeutic benefit.

Treatment of neurological disturbances

As the neurological phenomena, particularly the prolonged muscular hypertonia, evoked by thioproperazine were considered to be essential to successful treatment, no efforts were made to combat them. Excitomotor attacks, and the parkinsonism sometimes seen in maintenance treatment, were however treated as follows:

(a) *Excitomotor attacks*

Benztropine (2 mg. orally), promethazine (50 mg. intramuscularly), and paraldehyde (5 c.c. intramuscularly) were each found to be equally satisfactory in rapidly aborting excitomotor attacks. The two anti-parkinsonism agents proved disadvantageous in that their action interfered with the production of prolonged muscular hypertonus. Paraldehyde, on the other hand, was far less troublesome in this respect and thus became our drug of choice for dealing with the attacks.

Suggestion was used on two patients late in the course. It was very successful in aborting attacks and appeared to be valuable in preventing any repetition. Furthermore, it had the great advantage of not interfering with the progress of the treatment.

(b) *Parkinsonism*

When parkinsonism was encountered during maintenance treatment, reduction of the daily dosage of thioproperazine was often sufficient to eradicate the symptoms. If, however, the dosage could not be reduced without mental deterioration, anti-parkinsonism drugs were given concomitantly. For those patients in whom the condition was associated with mild overactivity, 25 mg. promethazine was given orally b.i.d., in those with normal or reduced activity, however, 1 mg. benztropine b.i.d. was found to be satisfactory.

Similarity between signs and symptoms evoked by thioproperazine and those reported with epidemic encephalitis

With the important exception that the disturbances caused by thioproperazine disappear without sequelae within a few days of cessation of treatment, the analogy between the signs and symptoms due to the drug and those seen in encephalitis supposedly due to a virus is remarkable. Below is a table showing some of the signs and symptoms of epidemic encephalitis against those evoked by thioproperazine, the order corresponding with those mentioned in this paper.

Comparison between Signs and Symptoms of Epidemic Encephalitis, as Recorded by Various Authors, and those evoked by Thioproperazine

<i>Symptoms or Signs reported in Epidemic Encephalitis</i>				<i>Source</i>	<i>No. of Male Patients showing similar Symptoms or Signs with Thio- properazine</i>
Akinetic state	..	..	..	Lévy (1922); Lhermitte (1923); von Economo (1931)	24
Akineto/hypertonic state	..	..	..		36
Hyperkineto/hypertonic state	..	..	..		20
Inversion of sleep rhythm	..	..	..	Many authors	13
Easy arousal	..	..	..	Lhermitte (1923); Walshe (1920)	15
Pallor of face	..	..	..	von Economo (1931)	8
Brightness of eyes	..	..	..	Lhermitte (1923)	13
Abnormal yawning	..	..	..	Marie and Lévy (1920); von Economo (1931)	13
Bradykinesia	..	..	..	Lhermitte (1923)	29
Hyperaesthesia of plantar tendrils	..	..	..	Papin <i>et al.</i> (1919)	14
Autonomic disturbances	..	..	..	Many authors	41

Abnormal muscular movements ..	Many authors	29
Disturbances of reflexes	Buzzard <i>et al.</i> (1919); Hunt (1921)	37
Akathisia	Lévy (1922); Lhermitte (1923); Sicard (1921 and 1923)	20
Non-intention tremors	Hunt (1921)	27
Choreiform movements	Lévy (1922); von Economo (1931)	27
Athetotic movements	Roger (1920)	12
Clonus	Leblanc <i>et al.</i> (1920); Lévy (1922)	11
Extensor plantar response ..	Leblanc <i>et al.</i> (1920); von Economo (1931)	14
Dysdiadochokinesis	von Economo (1931)	6
Ataxia	Hunt (1921); Walshe (1920); von Economo (1931)	3
Rombergism	von Economo (1931)	2
Weakness of limbs	von Economo (1931)	3
Cataleptiform behaviour	von Economo (1931)	10
Ocular disturbances	Many authors	15
Anaesthesias	Hunt (1921); Roger <i>et al.</i> (1920)	4
Incontinence and retention of urine	von Economo (1931)	10
Erythematous plaques	Porot (1921)	3
Joint pains	Lévy (1922); Papin <i>et al.</i> (1919)	15
Excitomotor disturbances	Marie and Lévy (1920); Marinesco <i>et al.</i> (1925); Roger (1921)	8
Heightened suggestibility during excitomotor disturbances ..	Marinesco <i>et al.</i> (1925)	6
Respiratory disturbances	Marie and Lévy (1920); Papin <i>et al.</i> (1919); von Economo (1931)	2

PART III. CORRELATION

IN the first part of this paper we described the singular therapeutic effect of thioproperazine in schizophrenic patients; and in the second, we enumerated and detailed the neurological manifestations which were evoked by the agent during treatment, both in chronological and semiological orders. Attention was drawn to the similarity existing between these neurological disturbances and those occurring during the course of encephalitis lethargica, and it may be added that every neurological manifestation that has been reported in von Economo's disease was reproduced, to a greater or lesser degree, during this clinical trial. It must be emphasized, however, that these drug-induced signs and symptoms, unlike some of those caused by the virus of epidemic encephalitis, were transitory, could be easily and completely effaced, and left absolutely no sequelae.

In the psychiatric field, further similarities between the symptoms caused by the virus and those actuated by the drug were seen, but they were largely confined to alterations in the level of consciousness and awareness. Thus the comparison ends there because, whereas the virus of epidemic encephalitis may provoke florid psychotic symptoms in previously normal individuals (von Economo, 1930), thioproperazine suppresses or eradicates such disturbances in psychotic patients.

For such close analogies to exist fortuitously seems unlikely. Rather they suggest a *modus operandi* of the drug and the virus alike on the same neural parts or systems, including perhaps the brain-stem reticular substance.

The results of this trial have demonstrated that a definite relationship exists between the frequency and quality of psychiatric improvement in the schizophrenics and the neurological signs and symptoms evoked by the drug. These disturbances invariably appeared during successful treatment, their extent being proportional to the quality of the psychiatric response. Conversely, early suppression of such phenomena during a course of treatment in our patients resulted in failure to produce psychiatric improvement.

To account for a relationship of this nature on the grounds of individual sensitivity to the drug, or of toxicity specific to certain parts of the central nervous system, would be but a partial, and therefore unsatisfactory, explanation. A more attractive theory, because of its comprehensive character, is that thioproperazine, by acting on the reticular activating system, modifies both motor and mental functions, just as other drugs have been shown to do by Rinaldi and Himwich (1955).

Our clinical findings seem to support this contention with objective neurological signs. A great many of those seen during treatment with thioproperazine are analogous with those resulting from reticular stimulation or from experimental interference with its function. The appearance of abnormal reflex patterns, similar to those seen in our study, are commonplace in experimentation with the reticular formation. Likewise, alterations in the level of consciousness are found to occur in such experiments and would appear to be akin to those we have outlined in this report.

Recent studies of the brain-stem have described this central system and its function. Caudally it influences the spinal-cord reflexes and activity; rostrally it affects the hypothalamus and the pituitary and thus the autonomic and neuro-endocrine systems; and also the neocortex, subserving higher sensory, motor, and intellectual function, where it increases and diminishes, relates and integrates neural activity (Magoun, 1950).

McCulloch and others (1946) have shown that descending reticulo-spinal tracts represent the final common pathway of the extra-pyramidal motor system. Thus the reticular substance facilitates or inhibits such diverse functions as: flexor and extensor reflexes (Lindsley *et al.* 1949); muscular tone (Eldred *et al.* 1953); and co-ordination of agonists and antagonists (Gernandt *et al.* 1955); each and all of which have been shown to be materially affected by treatment with thioproperazine.

Likewise, the afferent sensory system has been found to be influenced and modified by experimental work on the reticular formation (King *et al.* 1957), and the site involved has been suggested by Sharples and Jasper (1956) as being in the thalamic reticular substance. Again, alterations in sensory perception and afferent impulses have been described in our patients whilst receiving treatment.

Autonomic control by the descending reticular tracts via the hypo-

thalamus and bulb were discussed by Dell (1952); as has been shown, certain autonomic functions were very markedly altered by thiopropazine.

Considerable work on ascending reticular influence on affective behaviour, as mediated by the diencephalon and rhinencephalon, in experimental animals has been carried out. Although hardly applicable to humans, it is noteworthy that affective fluctuations were frequently observed during the treatment of "affect-less" schizophrenics.

Experimental work on the reticular substance by Morruzzi (1949) demonstrated E.E.G. changes corresponding with arousal to full wakefulness and attention in animals. Clinical experience with thiopropazine has shown that the mechanisms involved with arousal, wakefulness, and attention were all disturbed or modified during treatment. Somnolence with easy and rapid arousal, inversion of sleep rhythm, suppression of excito-motor symptoms by the re-direction of attention, and other factors showing an altered and alterable consciousness, have been observed during this study to a degree that, hitherto, has been described only as occurring in encephalitis lethargica.

From the evidence adduced above, it can be seen that the signs and symptoms evoked by thiopropazine, by von Economo's virus, and by experimental work on the reticular formation are similar. From this it could be postulated that the virus, by disturbing the reticular substance or its synaptic connections with other systems, evokes the symptoms of encephalitis lethargica; and that similar disturbances of a transitory nature, when evoked by thiopropazine, provoke a favourable influence on centres involved in the schizophrenic process. Such a hypothesis of drug action in the central nervous system, which needs to be tested experimentally, does not, however, allow any conclusions to be drawn as to the aetiology of schizophrenia, the symptoms of which can be so satisfactorily suppressed by thiopropazine.

SUMMARY AND COMMENT

A clinical trial of a new phenothiazine derivative, thiopropazine, was conducted at Long Grove Hospital over a period of 11 months. The chief aim was to examine the claims from abroad as to the value of the agent in the treatment of schizophrenia and acute mania. A secondary object was to determine whether the neurological disturbances evoked by the drug were of therapeutic value; or whether they were disadvantageous.

The results were most encouraging. Of 58 schizophrenic patients (42 males and 16 females), with an average duration of illness of over 10 years, 32 achieved total remission of schizophrenic symptoms; 10 were very much improved; 15 were improved; and 1 failed to respond. The 2 manic patients responded quickly and adequately. Results in the female group were not so good as in the male, partly because of the high proportion of leucotomized patients, and partly because a relatively greater number of them received the "continuous" rather than the "discontinuous" treatment. Thus the sex of the patient did not influence the results, nor did other factors such as age, duration, or the type of schizophrenia.

The discontinuous method, with periods of active treatment interrupted by periods in which no drug was given, was employed in the great majority of cases. The duration of the active courses and of the intervals was determined by the degree and extent of drug-induced muscular hypertonia in the former, and by the speed at which this symptom disappeared after withdrawal of the drug. Thus the regimen for individual patients was not difficult to arrange.

Certain signs or symptoms occurring during courses were found to be of prognostic value as to the ultimate outcome. In the psychiatric sphere these consisted of: precocious mental improvement; reappearance of florid symptoms in withdrawn patients; and mood-swings between euphoria and depression; all of which were of good omen. In the somatic sphere, the development of widespread, marked muscular hypertonia generally presaged a favourable outcome.

Hallucinations yielded more rapidly and readily to the treatment than other symptoms; whilst fixed, paranoid delusions were the most resistive. Owing to the power of the drug to increase suggestibility, however, these latter symptoms could be dissipated with relative ease by psychotherapy.

Neurological disturbances of a remarkably protean nature were encountered in all but one of the patients. A close study of these was made in the 42 male patients. Of the many and diverse signs, that one alone which could be correlated with psychiatric improvement was muscular hypertonia: if this did not appear, or was suppressed by anti-parkinsonism drugs, there was little likelihood of success.

These disturbances closely resembled those described as occurring in epidemic encephalitis, and indeed the appearance of three roughly circumscribed syndromes—the akinetic state; the akineto-hypertonic state; and the hyperkineto-hypertonic state—similar to those recorded by Lhermitte and others, were recognized. Because of this analogy, an attempt has been made to correlate the two conditions by postulating a similar site of action for both von Economo's virus and the drug: namely, the brain-stem reticular formation.

Complications encountered were relatively few despite the remarkable potency of the agent. Three cases of hypostatic-type pneumonia occurred. These appeared in the early days of the trial and were probably due to the combination of akinesia and increased secretions. They were quickly and easily dispelled by antibiotics. Transitory incontinence occurred in 7 males and in a further 2 there was temporary retention of urine. Other minor complications included herpes labialis and conjunctivitis, in 5 and 4 cases respectively. There were no blood dyscrasias nor disturbances of liver-function; neither was there any hypotension at any time during the trial.

Thus, thioproperazine has been found to be of very considerable value in the treatment of schizophrenia, and, so far as our very small number goes, in acute mania. Because of its high potency and of the particular method employed to obtain the best results, however, we would suggest that, for the time being, its use in active treatment be restricted to hospitals so that adequate medical and nursing supervision can be provided.

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Reviews

Mental Subnormality. By W. A. HEATON-WARD. John Wright & Sons, Ltd., Bristol.

This little book gives a brief account of the causes and degrees of mental subnormality, with a short section on the developing child, mental tests, mental illness in the mentally subnormal, epilepsy and community and hospital care. The relevant provisions of the Mental Health Act are outlined.

The choice of the terms "primary amentia" and "secondary amentia" is unfortunate, as this terminology is outmoded, and a phrase such as "simple undifferentiated amentia" should not be used in 1960.

The section on Hospital training is also somewhat old-fashioned, mentioning domestic work and residential domestic posts for females and farm training schemes for males. There is no reference to the rapidly-growing facilities in hospitals for training in light industrial work, subcontracted from factories, such as making cake-boxes, assembling radio parts, toy making and scores of other jobs of a simple repetitive type for which there is wide scope for subsequent employment in the community.

The book may be of some value to those requiring a quick orientation in this field.

B. W. RICHARDS.

The Integrity of the Personality. By ANTHONY STORR. Heinemann, London, 1960. Pp. 174. Price 15s.

The author of this short and intriguing book is a consultant psychiatrist and analytical psychotherapist of the Jungian school. His aim is to define in simple terms the basic assumptions upon which his practice of psychiatry and psychotherapy rests. In this he has succeeded, and the personal and subjective quality of his writing combined with the clarity of his formulations make this a refreshing and readable document, the more so because it concerns an area where "scientific" and "objective" are still too frequently equated. Dr. Storr hopes that his book may contribute towards understanding of the psychotherapeutic relationship; in the sense that he has conveyed vividly and sympathetically some important principles about the dynamics of the psychotherapeutic process and the meaning of psychotherapy within the framework of Jung's idea of "individuation", his hope is justified. There must be few books that have both the width of perspective and the grounding in clinical practice.

Despite this, its appeal is likely to be extensive, rather than intensive. This does not mean that it is superficial, but rather that the width of the perspective that the author has chosen precludes any serious examination of the sort of problems that occupy psychotherapists and are of the most interest from the point of view of research and future understanding. Thus, practising analysts are likely to be disappointed by a statement such as "... the degree of recovery which takes place in the patient is proportional to the degree of maturity of the relationship which he is enabled to make with the therapist". From the point of view of the patient at the end of a successful analysis this is important and true, but many analysts would claim that the really interesting and important changes which can occur are those which seem to be proportional to the degree of immaturity of the relationship that the patient is able to make with the therapist.

The author, however, is well aware of the importance of the therapeutic regression as a "reculer pour mieux sauter", and the real problem is the level of the audience to which the book is addressed. The informed layman should find it outstanding, but might have a little trouble in negotiating some of the technical aspects of projective identification. Psychiatrists may value it most for the clear way in which Jung's

prospective view of mental illness is presented. The positive attitude to neurosis as a frustrated attempt at self-realization; the compensatory function of the unconscious; the view that many symptoms are not evils to be banished so much as signposts to mental contents that are clamouring to be integrated; these are amongst the topics that Dr. Storr discusses very well. His own views on the significance of incest, the relationship of dependency to aggression and the meaning of fascination are of considerable interest. He finds Fairbairn's theories valuable and makes use of them in his task of delineating the factors that he believes are common to all schools of psychotherapy. It is a pity that his perspective also precludes some study of the way in which the Jungian approach seems to differ quite widely from other schools. The archetype concept is mentioned briefly, but there is no reference in the index to either symbol or archetype.

One of the best chapters deals with the difference between analytic and non-analytic psychotherapy, and between analysis and indoctrination. This is of particular interest in the light of the late Professor Kennedy's recent observations on the subject.

MURRAY JACKSON.

Trifluoperazine, Clinical and Pharmacological Aspects. Introduced by HENRY BRILL, M.D. Published by Lea & Febiger, 1958 (U.S.A.), and Henry Kimpton, 1959 (London). Pp. 219. Price 26s.

This "monograph" on Trifluoperazine (Stelazine) consists of 25 reports from the United States and Canada on various aspects of the drug. The book contains useful information on the pharmacological properties of the drug, its side-effects and toxic reactions and about the management of the latter.

It is difficult to accept uncritically the conclusions of the many clinical reports regarding the high efficacy of the drug in various psychiatric and organic disorders, because on the whole, the reports are impressionistic and do not reach the standard of precision and scrutiny which one expects these days, with drug trials. Some of the illustrative case reports, however, are informative.

N. H. RATHOD.

Trance in Bali. By JANE BELO. Oxford University Press, London, 1960. Price 60s. net.

In the 1930s Jane Belo lived in Bali for eight years, working for part of the time with Margaret Mead and Gregory Bateson. She became familiarized with all aspects of Balinese culture, and this book records her detailed study of the complex set of trances in existence at that time. This is a unique study of an institution that is rapidly changing, though despite the disturbances produced by the War, the ceremonies persist. This book describes the people who practise the trances. They were interviewed before and after the trances, and the dissociative nature of the states clearly shown. The actual trances were closely observed on film, and by note-taking by three Balinese secretaries against a time scale. The descriptions of these trance states account for the bulk of the book. The performances of the various types of trance were scheduled in accordance with the religious life and were a means whereby the Gods of Good and Evil could be communicated with, thereby relieving communal anxiety. This function of the trance ceremonies is particularly stressed.

While the trances are considered to be hysterical in character, the "players" are not regarded as hysterics. It is interesting that only certain individuals in that culture "who differed from their fellow villagers by a high emotionality, a lively imagination and, in general, a somewhat infantile psychic structure" were capable of going into a trance. Yet psychological tests given to a group of trancers and non-trancers revealed no differences between the groups, and it was concluded that the trancers could not be classed as "abnormal" personalities.

The book makes interesting general reading, reminding the reader of the wide range of dissociative phenomena that can be "normal" within a particular cultural setting, while for the specialized reader the detailed description of the various trance states remains unique.

B. M. DAVIES.

Crime Documentaries: 1. Guenther Podola. By RUPERT FURNEAUX. London: Stevens and Sons, 1960.

The arrest and trial of Guenther Podola for the murder of Detective Sergeant Purdy caused as great a sensation and as much controversy in this country as had any previous murder case. It is gratifying, therefore, that so experienced and skilful an author as Rupert Furneaux should have assembled the facts of this particular case in book form. The murder of a policeman whilst in the exercise of his duty is always regarded by the public with horror, but when subsequently the murderer puts forward a defence unique in the history of English Criminal Law we are clearly dealing with a case of compelling interest.

The author details the events leading up to the crime, the subsequent arrest, the events occurring whilst the prisoner was in hospital and on remand at Brixton Prison and finally describes the trial at the Central Criminal Court. Most of the information is factual but it has been assembled and arranged so as to be interesting and readable. It is perhaps unfortunate that the author sometimes includes his own comments and surmises, with which one may not always agree. At the time of the arrest rumours were current that the accused had been roughly handled by the Police and even that he had been "beaten up" at the Police Station. Questions in the House of Commons did nothing to relieve these fears. The actual events described, however, remove any doubts that the injuries sustained by Podola were other than accidental. Many days were spent at the trial in determining whether the amnesia claimed by the accused was genuine or feigned and the author has skilfully made a résumé of the evidence of each of the medical witnesses, quoting verbatim where necessary. But, as he says, "reading a murder case, months after its conclusion, is a very different matter to having to come to a decision at the time of the trial". It is difficult in print adequately to describe gestures, inflections or stresses used by the Judge, Counsel, or witnesses, which so frequently have important effects on the Jury.

As is well known, the medical evidence in this case was conflicting, not only in the opinions expressed, but in the criteria necessary to form an opinion as to the nature of the amnesia. The reader is unlikely to be able to reach a decision after reading the evidence, and Mr. Furneaux's summing up in the last chapter does not help clarification. Allegations of amnesia are not unduly rare in forensic work and are usually best tested by long and close observation of all the prisoner does and says both before and after trial. One cannot help wondering how Podola acted in the cells at the Old Bailey and while awaiting execution, though naturally the author had no access to this kind of information. It is within the reviewer's experience that one of the most convincing displays of hysterical amnesia was admitted as being feigned when the prisoner was seen immediately after sentence in his cell at the Central Criminal Court.

An attempt to paint the trial scene in rather melodramatic fashion occasionally spoils the more factual account, though this may help, and be appreciated by the reader with little or no experience of criminal trials. Probably the most interesting and valuable chapter is that dealing with the proceedings in the Court of Criminal Appeal, which the author reduces to language easily understandable to the average reader. It brings out the anticlimax of this case, when the Court ruled that "even if the loss of memory had been a genuine loss of memory that did not itself render the appellant insane so that he could not be tried on the indictment". It is the first time that a plea of unfitness for trial because of loss of memory has been put forward in English Criminal Law, and it may well be the last. However perplexed one may be by the differing opinions of the various medical witnesses, the book makes fascinating reading and is a valuable addition to the studies of those criminal cases in which important psychiatric problems have been raised.

F. H. TAYLOR.

The Registrar General's Statistical Review of England and Wales for the Three Years 1954-1956. Supplement on Mental Health.

This supplement is the fourth in a series starting with the year 1949. Anomalies and omissions which detracted from the usefulness of earlier editions have been successfully dealt with and it seems likely that this will be the form of presentation in future publications.

The first part contains summary tables with comments on interesting features. It is designed to show trends in mental hospital practice and confirms the general impression that although admission and discharge rates continue to rise the number of patients on the books of mental hospitals is declining. In addition it brings out clearly less obvious and less generally acknowledged features such as the anomalies in first admission rates for schizophrenia when considered in relation to the variables of age, sex, social class, and place of residence. In so doing it suggests subjects for extended study and to assist those wishing to pursue this type of enquiry the second half of the supplement gives detailed appendix tables.

The delay in preparation and publication is disappointing. An annual supplement covering one year might possibly be considered and the calculated omission of figures for the non-statutory or informal type of admission should soon be reconsidered.

LINDSAY WALKER.

Epidemiology of Mental Disorders. Eighth Report of the Expert Committee on Mental Health. World Health Organization: Technical Report Series, No. 185. 29 pp., price 1s. 9d. Also published in French and Spanish.

The epidemiological study of mental disorders has been relatively neglected in Great Britain. The important Scandinavian and American work does not receive much attention in D.P.M. courses, and questions on the subject are rarely asked in the examinations. However, the status of psychiatric epidemiology in Britain has begun to improve since the setting up of the Epidemiological Committee of the Medical Research Council; and the present Technical Report of the W.H.O. Expert Committee on Mental Health will be of great help in indicating the guiding principles for research in this subject and the practical ways in which such research should be organized.

The Committee emphasize the potential value of epidemiological studies, both for the intelligent administration of psychiatric services and for basic research into the aetiology and evolution of mental disorder. They recognize, however, that for a number of reasons progress is at first likely to be slow and hesitant.

Classification and diagnosis (especially in child psychiatry) present one of the largest difficulties. As regards classification, it is to be hoped that the W.H.O. Expert Committee on Health Statistics will provide a scheme which, unlike the current classification, will be internationally acceptable. As regards diagnosis, the Committee suggest that each case should be assessed at three levels—symptoms (anxiety, depression, etc.), syndromes (neurosis, psychosis, etc.) and diagnostic entities. The thorny problem of what constitutes a “case” is discussed and a working definition, in terms of loss of social capacity, is offered. The further useful suggestion is made that psychiatrists doing field work should rate the degree of certainty that a subject is a “case”.

The Committee think it reasonable that medical students, nurses, social workers and psychology students should take part in epidemiological surveys. Such experience might well form a valuable part of the training of mental health workers. Special training will be needed for research staff, and the Committee outline the training scheme they consider would be essential for psychiatrists. The report ends with a section on suggestions for research.

Everyone interested in the furtherance of epidemiological studies should read this brief but admirably clear report.

E. H. HARE.

The Teaching and Learning of Psychotherapy. By RUDOLPH EKSTEIN and ROBERT WALLENSTEIN. Imago Publishing Co., Ltd., London Pp. 334, price 42s.

The authors of this book are concerned with the teaching and learning of psychotherapy. They describe their experiences with doctors learning psychotherapy, and they particularly stress initial responses (including resistances) to learning. Despite the fact that the doctors had already shown their ability to learn in other fields and were voluntarily seeking psychotherapeutic skill, situations arise frequently, the authors noted, in which *at first glance*, the would-be learner psychotherapist appeared to be very ill. They noted too that problems of the teacher and others played a role in this assessment. They found frequently in such situations, that a complex interplay of interpersonal relationships between all the participants had highlighted a significant conflict of the *patient*, the one who was really ill. The authors' thesis is that such problems arise from "the way a particular individual attempts to master a new experience and to incorporate the new without doing too much violence to the old". The authors show with many excellent examples ways and means whereby both learners and teachers become aware of and are able to handle such problems without, of necessity, long term analysis of the deepest internal conflicts of the participants. At one point, the authors describe a situation in which a student psychotherapist is in difficulties. They point out four different possible ways of handling the situation:

1. The student could be considered sick and in need of analysis.
2. The student could be considered uninformed and in need of didactic instruction.
3. The student could be considered to have a countertransference problem and analysis of that particular countertransference would alter the situation.
4. The student could be seen to have a problem about learning with the teacher—a transference problem.

Certainly these four possible ways summarize excellently problems about learning and the authors' main plea is that the fourth method be given full consideration with the hope that "a flexible generation of teachers will be willing to make choices among these four possible models, choices deriving from the specific problems and needs of the learner rather than from the teachers' personal preferences and their personal security as teachers". The detailed accounts of the work carried out justify the techniques used and thus open out a rich and valuable field in which highly rewarding results occur.

The authors are to be congratulated on a presentation which is clear and easy to follow. As always, in dedicated workers, their intense interest in and enthusiasm for their ideas emerge fully and must be recognized as factors in the results achieved. Nevertheless, their vision is wide with no rigidity or binding to fixed theories, and they make no claim to finality.

They point out that "psycho-analysis can increasingly be seen as a constantly interacting process in which concern with defensive constellations and with instinct derivatives are only the alternating sides of the same coin and at the end of which a process has been worked through, a process in which each of the aspects of mental activity has been seen in all its interlocking relations with the other, and none is by itself the single cause". With this approach to mental activity the teaching and learning of psychotherapy, as described in this book, fall very well into place.

J. L. ROWLEY.

THE ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION

THE RECRUITMENT AND TRAINING OF THE CHILD PSYCHIATRIST

(Approved by Council 11 February, 1960)

The Child Psychiatry Section of the Royal Medico-Psychological Association, which is the professional body of child psychiatrists in this country, considers the present to be an eminently suitable time for a reassessment of the recruitment and training of child psychiatrists.

As a result of the Report of the Committee on Maladjusted Children, circulars have been issued by the Ministry of Health and the Ministry of Education, making recommendations in the fields of child guidance and child psychiatry. The implementation of these circulars will call for an expanded service, and hence an increase in the establishment of child psychiatrists. Again, the Mental Health Bill is a stimulus to psychiatry generally and will lead to an expansion of the Mental Health Services. The Royal Medico-Psychological Association is desirous, not only of attracting a sufficient number of trainee child psychiatrists into the field, but also of attracting doctors of high ability into the field of child psychiatry and making it possible for them to receive a sound training so that consultant appointments will attract applicants of adequate training and experience.

The supply of child psychiatrists was reviewed by the Royal Medico-Psychological Association in a comprehensive document in 1951 (1). A brief memorandum was also addressed to the Ministry of Health in June, 1955 (2), and the helpful attitude of the Ministry at that time has encouraged the Royal Medico-Psychological Association to review the matter again.

In considering the functions of child psychiatrists reference should be made to the memorandum of the Royal Medico-Psychological Association published in 1951 (1). The views expressed therein have been amplified by two later documents (3, 4). Briefly, these functions include clinical work in out-patient child guidance and child psychiatry clinics, clinical work in in-patient units, teaching, research, and preventive work in the community. Work with the pre-school child, the school child, the adolescent, and the parents is involved.

SUPPLY OF CHILD PSYCHIATRISTS

(a) *Estimation of the number required.*

The population to be served in England and Wales is approximately 40,000,000, in Scotland approximately 5,000,000 and in Northern Ireland approximately 1,000,000.

After careful consideration and enquiry of its members, the Royal Medico-Psychological Association regards a realistic minimum estimate to be, that one full-time, trained child psychiatrist, with complementary junior psychiatric staff, is required per 200,000 of the population, i.e., 200 child psychiatrists for England and Wales, 25 child psychiatrists for Scotland, and 5 child psychiatrists for Northern Ireland—a total of 230 child psychiatrists. But future experience will probably show that this is an under-estimate of the minimum number required.

(b) *Numbers available*

(i) *Consultants and S.H.M.Os.* The Underwood Report (5) estimates that in December, 1954, there were the equivalent of 56 full-time psychiatrists employed by local authorities and that in December, 1951, there were 39 psychiatrists employed by the hospital service, the total, therefore, being 95 full-time child psychiatrists.

An analysis now by the Royal Medico-Psychological Association of the

directory of child guidance clinics published by the National Association of Mental Health in 1958 showed that, at an optimistic estimate, the equivalent of approximately 160 full-time child psychiatrists were being employed in local authority clinics, hospital clinics, and teaching hospital clinics in England, Wales, Scotland and Northern Ireland. Not all these psychiatrists were graded as consultants.

An R.M.P.A. survey of 1953 throws some light on the grading of child psychiatrists. Of the 89 child psychiatrists who replied to a questionnaire, 68 were consultants, 18 S.H.M.O.s., and 13 were ungraded. Two-thirds of those in charge of local clinics were consultants and all those in charge of clinics in teaching hospitals were consultants. It is the policy of the Royal Medico-Psychological Association to advocate that any psychiatrist in charge of a clinic should be graded as a full consultant.

An analysis of the advertisements for the four years 1950-53 showed that there was a tendency for a disproportionate number of S.H.M.O.s. to be appointed. This is to be deprecated, especially since it has led to S.H.M.O.s being left in charge of clinics, and because it has had a most adverse effect on the recruitment of child psychiatrists.

(ii) *Senior Registrars.* A Royal Medico-Psychological Association estimate of 1955 showed that there were four and a half senior registrars unevenly distributed outside London, and six senior registrars in London, making ten and a half senior registrars in England, Wales and Scotland. Since then it is estimated that approximately five additional senior registrar appointments have been made. Thus there is a total of approximately 16 senior registrars in child psychiatry.

The table made available by the Ministry of Health and the Department of Health for Scotland in 1958 (*British Medical Journal*, ii, Supplement, p. 139) showed that the ratio of training posts to consultants in mental health generally, is approximately 1 to 5, and in all specialties 1 to 6. From the data given above it will be seen that the ratio in child psychiatry is 16 to 160, i.e., 1 to 10.

(iii) *Registrars.* A Royal Medico-Psychological Association estimate in 1953 showed that there were $3\frac{1}{2}$ registrars in the provinces and 16 in London, making a total of $19\frac{1}{2}$ registrars engaged in child psychiatry throughout England, Wales and Scotland. This grade is not normally suitable for trainee child psychiatrists, but offers an opportunity for a psychiatrist undergoing general training to have training in child psychiatry.

(c) *The Need for Training Posts*

Training posts are required in child psychiatry for the following reasons:

- (1) To maintain the present number of child psychiatrists, by making good the losses through death, retirement and transfer.
- (2) To make up the backlog and provide for the optimum number within the next five years—the longest period that can reasonably be allowed for the task.
- (3) To provide extra consultants in teaching clinics.
- (4) To make some consultants available for clinical research in the field.

Earlier in this document it has been estimated that a minimum of 230 child psychiatrists is required, and that approximately 160 are available. Thus 70 additional senior posts are required.

It is assumed that 16 senior registrar training posts are established at the moment. The addition of 24 senior registrar posts would make a total of 40 senior registrar training posts. Training takes three years, and thus about 14 child psychiatrists would be produced per year. In five years approximately 70 child psychiatrists would be forthcoming, and this with the existing 160 child psychiatrists would make a total of 230 child psychiatrists, which is the desirable optimum

number, making the ratio of training posts to consultant posts 40 to 230, i.e., *nearly 1 to 6*. The above figures do not take account of the need to make good the losses due to retirement, etc., during the next five years, and this factor together with the time required to establish new training posts may cause the programme to extend beyond the five years suggested above. However, the programme may be helped by the candidates who, exceptionally, may be so qualified that they can complete their training in less than three years.

The 24 extra training posts could be provided by doubling the number of existing senior registrar posts in clinics already offering training facilities, and by creating training posts where there are suitable facilities in other clinics. There are grounds for believing that recruits are forthcoming. The extra 24 posts will need retention at the end of the five year programme so as to maintain the desirable ratio of training posts to consultant posts at 1 to 6. The position should be reviewed at the end of a further five years.

(d) *Recruitment*

The majority of child psychiatrists are likely to be recruited from the field of general psychiatry. Thus all the factors affecting the recruitment of general psychiatrists eventually impinge upon the recruitment of child psychiatrists. These include the changed attitude of the public towards psychiatry, the sounder training in psychiatry for medical students, training facilities, the availability of posts in general psychiatry, and the equitable distribution of merit awards.

In addition there are factors more directly related to recruitment into child psychiatry. These include the opportunity for some training in child psychiatry for the medical student, the availability of a period of training in child psychiatry extending over at least six months for the general psychiatrist, opportunities for promotion equal to those in other professions, availability of training posts in child psychiatry, proper conditions of clinical work, and opportunities for original work in this field.

It is known to the Royal Medico-Psychological Association that excellent recruits have been obtained in the past from paediatrics, public health, general practice and general medicine. Every encouragement should be given to facilitate transfers from these disciplines, although it is emphasized that training should take place in two stages:

- (1) A comprehensive training in general psychiatry, with particular attention to the understanding, management and treatment of the neurotic patient.
- (2) Specialized training in child psychiatry.

TRAINING

This has been outlined in detail in the memorandum of 1951 (1).

The memorandum envisaged a comprehensive basic training in general psychiatry at the senior house officer and registrar levels. Specialization in child psychiatry should normally take place at the senior registrar level and a three year period of training at this level was recommended.

In the years since this memorandum was published experience has shown that particular attention must be paid to training child psychiatrists in the understanding and treatment of the psychopathology of both the child and the adult neurotic patient.

The specialized training required at the senior registrar level for the trainee child psychiatrist should be undertaken at clinics orientated towards teaching and research, which are able to offer a comprehensive training, with a consultant child psychiatrist in charge, and with the clinic having sufficient staff to allow adequate time for the supervision of its trainees. The establishment of consultant psychiatrists in training clinics should be greater, in order to allow time for teaching.

RECOMMENDATION

In order to produce the desirable optimum number of child psychiatrists in the next five years the Royal Medico-Psychological Association recommends the immediate establishment of 24 additional senior registrar training posts in child psychiatry.

REFERENCES

- (1) Memorandum on the Training of the Consultant Child Psychiatrist, 1951. Royal Medico-Psychological Association.
- (2) Memorandum on Training Facilities for Consultant Status in Child Psychiatry in Great Britain, 1955. Royal Medico-Psychological Association.
- (3) Organization of Psychiatric Services for Children and Adolescents, 1956. Royal Medico-Psychological Association.
- (4) Memorandum on the Report of the Committee on Maladjusted Children, 1957. Royal Medico-Psychological Association.
- (5) Report of the Committee on Maladjusted Children, 1955. Ministry of Education. H.M.S.O.

MEMORANDUM ON

UNITS FOR THE LONG-TERM MEDICAL CARE OF EMOTIONALLY DISTURBED CHILDREN AND ADOLESCENTS

(Approved by Council 3 May, 1960)

In September, 1956, the Child Psychiatry Section of the Royal Medico-Psychological Association in its memorandum on "In-Patient Care of Child and Adolescent Psychiatric Patients" dealt in detail with the provision of units for the short-term investigation and treatment of children and adolescents. It also drew attention to the need of "increased provision of long-term substitute home care for disturbed children" and "improved provision of after-care hostels for adolescent patients" as was forecast in Section of 17 of the National Health Service Act, 1946, and in the memorandum to Regional Hospital Boards (47) 13, para. 38.

It is being increasingly recognized that the adequate care of adult psychiatric patients requires, in addition to hospital in-patient and out-patient units a variety of establishments not previously considered essential, in particular the day hospital, the hostel, and the protected workshop. A corresponding range is required for children and adolescents. The Child Psychiatry Section considers that the stage has now been reached for further thought to be given to the provision of units for the long-term medical care of disturbed children and adolescents, and as a start, the setting up of one or more such units as prototypes.

The Problem

We are concerned with children whose needs are not appropriately met by schools for maladjusted children nor by in-patient treatment in a Children's Psychiatric Unit. Some may not have needed admission to an in-patient ward in the first place; others may have had a period of in-patient treatment and made a partial recovery.

The children we have in mind are likely to respond slowly to care and treatment and to need progressively a less medical setting.

They are not a homogeneous group. There will be a considerable range of age and intelligence although the severely sub-normal child is not here included. Some are children with some abnormality of brain structure or biochemical disturbance; some have been seriously affected by psychological or social disturbance; many have elements of both. These children may show such symptoms as bizarre behaviour, the restlessness and fantasies of the deeply disturbed, running away, impulsive acting out of sex problems and fire-raising which make them unsuitable for a school.

To be deemed long-term it is presumed that they will need at least twelve months residence away from home, and in fact they may require several years of slowly diminishing care until they are able to take their place in the community.

Present Position.

Children are admitted to Psychiatric In-Patient Units for Children only when their disorders are severe. They may stay in hospital for months or years. Hospital treatment may take any of a number of specific forms, but has certain general characteristics which are important to our present suggestions.

The Children's Psychiatric In-Patient Units at present available are medically directed, patient-centred and tolerant of the child's symptoms and disturbed behaviour. In contrast to these, most schools for maladjusted children are essentially schools which, however much they may have the emotional adjustment of the individual child as their concern, may be obliged to put more emphasis on the educational attainments of the group. The homes from which these children come will not be able to give the patient the attention he needs, for in them are others with conflicting needs; demands are, almost inevitably, made on the child which he cannot fulfil, and equally, he makes demands which cannot be met, so serious difficulties arise.

Proposals

To help meet the problem we suggest that in addition to psychiatric in-patient units for children, there is a need of two further kinds of units:

- (1) Hospital Annexe.
- (2) Therapeutic Hostel.

The Hospital Annexe would be a unit devised to meet the needs of children who, though developing, are suffering from distortions of personality, and in particular, have serious difficulty in making relationships with other people. Such a unit should be so staffed and equipped that children in them can try out their feeling relationships, first with adults, and later with one another. It should be a unit where the maturing of the personality takes precedence over learning in the school sense or working in the sense of employment. It should be an annexe to a hospital with a psychiatric in-patient unit for children to which patients could be returned without formality should their condition deteriorate. Every effort should be made to maintain contact between children and their parents. Since a hospital annexe will necessarily serve a large area, most of the children in them will be a long way from their homes. For this reason, accessibility and ease of communications should be given most careful consideration when the site of the unit is being chosen.

The Therapeutic Hostel, a quite separate undertaking, would be for those children and adolescents who are able to enter the competitive community of everyday life in working hours, but still require shelter and therapy for the remainder of the day. Some individuals as they mature are able to achieve a reasonable standard of work while still needing help with their personal relationships.

Proposed Hospital Annexe

The needs and interests of children vary with their age, constitution, intelligence and previous experience, and it is customary to differentiate a young group from, say, age seven to twelve when the ages can be mixed, a middle group twelve to sixteen (the school leaving age for maladjusted children) and thirdly, the older adolescent. These divisions cannot be hard and fast, but puberty and education inevitably affect to some degree the internal arrangements and staffing of any establishment which covers the age range of 7 to 17 years.

As the needs of the patients are neither for a hospital nor for a school, it is

difficult effectively to convert present buildings and, as buildings inevitably influence use, it is considered that a new building will have to be constructed and that architects and doctors will have to co-operate imaginatively over its design. Since this unit requires considerable free acreage around it, it will have to be located some distance away from the parent-hospital and should be planned on the lines of small family units with the furniture, fittings and equipment specially chosen, keeping in mind the devastating destructiveness of a few of these children. Dirt and aggression have their place in a therapeutic environment. Some of these children tend to be hyperactive; they require extensive floor space if they are not to feel hemmed in and frustrated.

It has been the experience of many medical administrators, that the larger the group the harder it is to keep an intimate personal atmosphere and as it is this atmosphere that is one of the major therapeutic tools, a unit must not be allowed to become over-full or cramped. Further, the larger the area drawn from, the harder it is for parents to visit and every effort should be made to maintain contacts with the parents to encourage them to stay near the unit, and, if practicable, to have their children home for holidays.

It is recommended that such an annexe should be divided up into small units, forming, as far as possible, "Family groups"; such providing altogether, for administrative convenience, an Annexe of 30 to 50 children, divided into suitable groups not exceeding 10 in each.

Staff

A high staff-patient ratio is necessary. The internal staff arrangements of these units should be such as to reduce as far as possible the number of adults in contact with any one child. In other countries and in a few residential units in this country, the trained staff, looking on their work as a vocation, are as flexible in taking time off as the average mother. This continuity and sense of purpose is of the greatest therapeutic value to the disturbed child.

Types of staff needed include:

- (a) Those whose basic training is medical, e.g., doctors, psychotherapists, nurses.
- (b) Those whose basic training is social, e.g., psychiatric social workers.
- (c) House-parents.
- (d) Those whose basic training is academic, educational or vocational, e.g., psychologists, teachers, house-craft and workshop instructors, occupational therapists.
- (e) Clerical, domestic, gardening and maintenance staff.

The number and type of workers will vary with the size of the unit, some may be part-time, others shared with the parent hospital. Nursing staff should not, however, be rotated, but should, as far as possible, be permanently attached to the Annexe. The personal suitability of the staff for this exacting type of work is more important than the form of their professional training and the head of the unit should be given considerable latitude in selecting staff. A quota of competently guided nursing cadets, with youth and enthusiasm on their side, may give very satisfactory service.

The staff of the Child Psychiatric Unit to which the Annexe is attached, should be sufficiently generous to provide adequate psychiatric time to be spent on the Annexe and also a sufficiency of Psychiatric Social Worker and Psychologist time. Ten house-parents, of whom some, preferably the majority, should have mental nursing training; five assistants, some of whom might have had Child Care or other suitable experience, and some of whom might be Nursing Cadets, and teachers or instructors would be required. Some night staff would be essential.

Proposed Therapeutic Hostel

It has long been recognized that certain handicapped individuals may be able to learn to work alongside others in the community yet require special facilities or training after working hours. The Night Hospital for neurotic patients, the Hostel for the severely sub-normal, are such places, and similar facilities are needed for emotionally disturbed children and adolescents. They may become either too indrawn or react explosively when frustrated by authority or stimulated by the opposite sex. Some of these are best helped by individual therapy, others require group therapy, but all require psychiatric supervision.

The warden, and preferably the deputy, should have had case-work training. The establishment for house-parents should allow for each pair having adequate time off each week. The children would normally eat in their own houses. There is much to be said for having married house-parents with their own families, but experience has shown that it is extremely difficult to find couples who both have the right temperament and interests in this kind of work.

Other Long-Term Care and Day Hospitals

In giving prominence to children and adolescents who need care in a Hospital Annexe or a Therapeutic Hostel and for whom the ultimate prognosis is fair, the needs of other groups of children should be kept in mind. There are, for instance, children and adolescents who require psychiatric treatment or supervision but who can spend part of their day in their own homes. For these we would like to see the concept of the Day Hospital extended and modified to meet the special needs of the young, and we should like to see more use made of short-term voluntary admission to a psychiatric hospital for the benefit of patients of this sort and their parents.

An equally important group is that of children and adolescents with a poor prognosis. Reference was made in the earlier memorandum to those needing care in a long-stay hospital, but we believe that this is another group for whom a special Annexe is preferable to a hospital. There is a serious dearth of attractive family units for children of this sort who at the moment are occupying beds which might be used for the active treatment of acutely ill patients.

Mental Health Act, 1959

The Mental Health Act, 1959, concerns itself not only with arrested and incomplete development of mind but also with "any other disorder or disability of mind". (Section 4.) The Act in Section 19 refers to Residential Homes as including establishments, "The sole or main object of which is, or is held out to be, the provision of accommodation, whether for reward or not, for persons suffering from mental disorder". In Section 147, medical treatment is stated to "include care and training under medical supervision". It is clear therefore that the Hospital Annexe and Therapeutic Hostels devised as they are for the "care and training under medical supervision", are within the province of the Ministry of Health.

JOINT S.F.A./R.M.P.A. FILM APPRAISAL PANEL*Summaries of Recent Films*

"*Marlborough House*". (16mm., sound, colour; approx. 15 minutes.)

A prize-winning film showing the life of mentally sub-normal patients at a local authority training centre, this film admirably succeeds in its purpose of gaining sympathy for this work. From: Mental Health Services, Marlborough House, Marlborough Hill, Bristol 1.

"A New Chapter". (16mm., black and white, sound; approx. 30 minutes.)

Describing the problems faced in the U.S.A. by a discharged mental hospital patient, this convincing film is of useful value in Great Britain with the booklet that goes with it. From: Messrs. Smith, Kline and French Laboratories Ltd., Welwyn Garden City, Herts.

"Remotivation". (16mm., sound, black and white; approx. 30 minutes.)

Showing the methods of the late Dorothy Hoskins Smith in awakening the interest of chronic mental patients in the U.S.A., the value of this interesting film is limited by its sound-track, though it has value in increasing the efficiency of assistant nurses. From: Messrs. Smith, Kline and French Laboratories Ltd., Welwyn Garden City, Herts.

"Psychiatric Nursing—The Nurse/Patient Relationship". (16mm., sound, black and white; approx. 30 minutes.)

Demonstrating how a psychiatric nurse should have a good relationship with a patient, and showing the mistakes which should be avoided, this beautifully acted film loses little of its value by originating in the U.S.A., and is excellent for discussion. From: Messrs. Smith, Kline and French Laboratories Ltd., Welwyn Garden City, Herts.

"Human Gastric Function". (16mm., sound, colour; approx. 25 minutes.)

Showing the reactions of the stomach mucosa over a period of fifteen years in the well-known case of "Tom", who had a traumatic gastric fistula, this film is a first-rate introduction to psychosomatic concepts. From: Smith, Kline and French Laboratories Ltd., Welwyn Garden City, Herts.

"Psychiatric Newsreel No. 1". (16mm., sound, black and white; approx. 20 minutes.)

Containing items mainly of American interest, its "popular" approach limits its appeal, and the last sequence is too long. From: Smith, Kline and French Laboratories Ltd., Welwyn Garden City, Herts.

"Play and Personality". (16mm., sound, black and white; approx. 30 minutes.)

Showing the development of the personalities of two children in free play situations, this discreetly photographed film very effectively illustrates the reactive nature of the children's behaviour disturbances, with their underlying mental mechanisms. From: The Cassel Hospital, Ham Common, Richmond, Surrey.